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APPLICATION NUMBER:

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SUMMARY REVIEW

Summary Review for Regulatory Action

Date	November 7, 2018
From	Theresa M. Michele, MD Director, Division of Nonprescription Drug Products
Subject	Division Director Summary Review
NDA/BLA #	205920 SD-73
Applicant Name	Armstrong Pharmaceuticals, Inc.
Date of Submission	May 7, 2018 (Class 2 Resubmission)
PDUFA Goal Date	November 7, 2018
Proprietary Name / Established (USAN) Name	Primatene Mist (epinephrine inhalation aerosol)
Dosage Forms / Route of Administration / Strength	Aerosol, metered / Inhalation / 125 mcg/actuation
Proposed Indication(s)	Temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older
Regulatory Action	Approval

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Epinephrine HFA is a short-acting bronchodilator for the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of the chest, and shortness of breath. OTC availability may provide benefit to consumers due to increased access to a short-acting rescue medication without requiring a prescription. For consumers with mild, intermittent asthma, being able to purchase a rescue inhaler in the OTC setting could supplement prescription medication for cases in which a prescription had run out or was unavailable. Efficacy and safety of the 125 mcg HFA product was demonstrated in asthma patients in a 12 week study with an additional 12 weeks of safety follow up. As expected, tachyphylaxis did occur in this trial after 12 weeks of continuous use, supporting the recommended as needed, intermittent dosing.

Key risks of epinephrine HFA include consumers not getting accurate dosing (or failure to receive a dose) due to use errors with the inhaler, cardiac safety, adverse asthma outcomes, and misuse and abuse contributing to cardiac and respiratory adverse events. While it will likely not be possible to completely eliminate use errors, at this point, I believe that labeling has been sufficiently optimized that consumers will be able to follow the instructions for use of the inhaler to obtain the correct delivered dose, and further optimization is unlikely to result in improvement. The dose of 125 mcg was chosen based on results of two dose ranging studies to deliver the lowest dose providing reliable efficacy to minimize adverse effects, and package size will be limited to a single inhaler with a maximum of 160 metered actuations (total of approximately 10 days of maximal use) to minimize overuse. A high dose PK study in healthy volunteers delineated the dose-related cardiac effects, suggesting that consumers would likely need to take about 5 times the maximum labeled dose at one time to get clinically important elevations, which is an adequate safety margin. In addition, the label includes a prominent asthma alert warning, a contraindication to use unless a doctor said you have asthma, and instructions to ask a doctor before use if you have ever been hospitalized for asthma, have heart disease, high blood pressure, or are taking prescription drugs for asthma, among other warnings.

The very long OTC marketing history and known adverse event profile of the CFC version of this product are supportive of the safety profile of the HFA product for OTC use. Taking these factors into account, the overall risk-benefit assessment supports OTC approval of epinephrine HFA for the temporary relief of mild symptoms of intermittent asthma for adults and children 12 years of age and older.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Asthma is a chronic inflammatory disease of the airways with reversible bronchial hyperreactivity. • Asthma is characterized by varying and recurring symptoms of shortness of breath, chest tightness, wheezing and cough, airflow obstruction, bronchial hyper-responsiveness, and underlying inflammation. • Asthma varies in severity, and terminology is evolving. The National Asthma Education and Prevention Program (NAEPP) classifies asthma based on level of symptoms, nighttime awakenings, bronchodilator use for symptom control, interference with normal activity, lung function, and risk of exacerbations. • NAEPP defines mild intermittent asthma as the mildest form of asthma. It can be treated with short-acting beta-agonist bronchodilators alone on an as needed basis. • Asthma exacerbations may be life-threatening and require prompt, appropriate treatment. Severe, life-threatening exacerbations may also occur in patients with mild asthma. Short-acting inhaled beta-agonists are generally the initial treatment for exacerbations. • A major limitation of this program is that self-selection studies were not conducted to determine whether consumers with more severe asthma or conditions other than asthma would select to use epinephrine HFA. In addition, an actual use study to evaluate misuse in a "real-world setting" was not conducted. 	<ul style="list-style-type: none"> • While asthma symptoms may be recognizable to a consumer, proper diagnosis requires a health care professional as symptoms of wheeze, cough, shortness of breath, and chest tightness may occur with a variety of other diseases. Pulmonary function testing is an expected part of diagnosis. • Labeling includes a contraindication not to use the product unless a doctor said you have asthma. • Severity of asthma may vary over time, and symptoms beyond mild intermittent require anti-inflammatory controller medication. • Patients who have a history of hospitalization due to asthma (especially those who were previously intubated) or who have conditions other than asthma may be especially vulnerable. • Labeling includes a prominent asthma warning. • Because this product was a reformulation, the application relied upon the long history of OTC use (since 1967) of epinephrine CFC to support consumer use for the labeled indication. This is not a generalizable conclusion for other OTC asthma applications.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	<ul style="list-style-type: none"> • The CFC epinephrine inhaler was phased off the market in 2011 due to environmental issues, not due to issues related to safety or efficacy. Since that time, there have been no OTC MDI options for asthma. • A number of asthma therapies exist in the prescription setting, including short-acting beta-agonists reliever/rescue medications (albuterol, levalbuterol) and controller medications (inhaled corticosteroids, montelukast, long-acting beta-agonists, and a variety of newer biologic agents for more refractory, severe disease). 	<ul style="list-style-type: none"> • An OTC rescue inhaler could benefit patients who are unable to obtain immediate medical treatment of their asthma symptoms, but are not having symptoms that would necessitate emergency medical care. • This could occur for a variety of reasons, such as running out of a prescription after normal business hours or travel.
Benefit	<ul style="list-style-type: none"> • Two dose ranging studies were conducted to choose the lowest dose with consistent effectiveness. • A 12-week phase 3 trial in adults and children down to age 12 with a 12 week safety extension demonstrated significant improvement in FEV1 after use of epinephrine HFA compared to placebo. Expected tachyphylaxis was demonstrated after 12 weeks of use, supporting intermittent, as needed dosing. • The phase 3 trial demonstrated a number of device failures that were determined to be related to use errors, suggesting that consumers would be unable to use the product effectively. Based on this, many iterative improvements to labeling were made to ensure that consumers could follow the instructions for use. • Due to issues with HFA inhaler designs, it is necessary to exactly follow the instructions for use, particularly with regard to shaking and spraying the product 4 times to prime the device, shaking and spraying one time prior to each inhalation, and cleaning the device after each day of use. Failure to follow these instructions results in variable dosing (overdose or underdose), which could affect safety and efficacy. • Multiple iterative label comprehension and human factors studies were conducted for this application, eventually honing in on the 3 key tasks to prevent device failures (priming, shake and spray prior to each dose, and daily cleaning). 	<ul style="list-style-type: none"> • Usability in the OTC setting is a key approvability issue given that this product is indicated for acute relief of asthma symptoms, which if not treated promptly may result in adverse asthma outcomes, including hospitalization and death. • Robust bench testing of the device was conducted to support labeling. The most conservative instructions were chosen to allow for some variation in user performance without resulting in clinically important device failures. • The final human factors study demonstrated adequate performance of key tasks, supporting approval. • It is unlikely that perfect adherence to labeled instructions is possible, but testing suggests that labeling has been maximally optimized.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> A 4 week efficacy trial in pediatric patients with asthma aged 4-11 years was conducted, but was underpowered and failed to demonstrate statistically significant efficacy. 	<ul style="list-style-type: none"> The label contains the following contraindication to use in children under the age of 12 years: Do not use. It is not known if the drug works or is safe in children under 12. The explanatory language was added because the epinephrine CFC product was approved down to age 4 years. There will be a post-marketing requirement under PREA to conduct another safety and efficacy trial in children aged 4 to under 12 years.
Risk and Risk Management	<ul style="list-style-type: none"> Because epinephrine is a non-selective beta-agonist, it is expected to have dose dependent sympathetic effects, including elevations in blood pressure and heart rate. Armstrong conducted two separate dose ranging studies to select the lowest dose providing consistent effectiveness. The high dose PK study in healthy volunteers demonstrated that increases in heart rate and blood pressure did not occur until doses of 1250 mcg (5 times the highest recommended dose) were reached, suggesting that consumers would need to use much more than the highest recommended dose to get these effects. No clinically important cardiac safety signals were observed in the Phase 3 trial. The short duration of action of epinephrine compared to prescription beta-agonists limit potential risks related to unopposed sympathomimetic effects and asthma-related deaths observed with high-dose, long-acting beta-agonists. Post-marketing safety reports for epinephrine CFC (Primatene Mist) were evaluated for a 15 year period (1997-2012), including specific consideration of cardiac adverse events, asthma-related adverse events and events related to misuse. During this time period, there were 116 serious adverse events 	<ul style="list-style-type: none"> PK and clinical trial data for epinephrine HFA are reassuring for cardiac safety if used according to the product label. Labeling will include a variety of warnings, the most important of which is the 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. There are also two contraindications (do not use) 1) unless a doctor said you have asthma, and 2) if you are now taking a prescription monoamine oxidase inhibitor. Given the limitations of post-marketing reporting, post-marketing adverse events do not suggest a particular safety issue related to use of the CFC product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>reported, including 41 deaths. Given limited information and various confounding factors, causality could not clearly be determined for these deaths. Twelve deaths included cardiac-related AEs, and 5 were related to abuse/misuse of the products. There were two deaths reported in children, one in a 10 year old boy who seized while in a pool, and one in a 17 year old female who died of an asthma exacerbation. The sponsor reports that there were 66 million units of epinephrine CFC distributed during this time period.</p> <ul style="list-style-type: none"> • Misuse of epinephrine HFA involves consumers using more than recommended on the product label in order to obtain symptom relief instead of seeking medical care. The obvious concern is that this could lead both to adverse asthma outcomes from failure to obtain appropriate escalation of therapy and tachyphylaxis to the beta-agonist effects with resultant asthma-related death, a known potential outcome of high dose beta-agonists. While this is a concern with any beta-agonist, the concern is heightened for an OTC product because therapy is not occurring under the supervision of a health care professional. 	<ul style="list-style-type: none"> • Because inhalers containing large numbers of doses or packaging of multiple inhalers together could potentially encourage consumers to use the product daily and delay health care provider visits, the package size of epinephrine HFA will be limited to immediate containers containing 160 metered sprays or fewer, with no more than a single inhaler packaged together, consistent with its intended use as a rescue medicine for occasional mild asthma symptoms.

1 INTRODUCTION

This supplement is a complete response to deficiencies identified during the first and second cycle for the 505(b)(2) application for NDA 205,920. In this application, Armstrong Pharmaceuticals, Inc. (Armstrong) is seeking approval for epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA), at a dose of 125 mcg/actuation for over the counter (OTC) use for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older.

Epinephrine-HFA is a short-acting beta₂-agonist (SABA) bronchodilator used as a quick relief medication for acute bronchospasm. Armstrong is positioning the epinephrine-HFA MDI (metered dose inhaler) as an alternative to the previously marketed Primatene[®] Mist epinephrine MDI, which was removed from the market in 2011 due to the phase out of ozone-depleting chlorofluorocarbon (CFC) propellants under the Montreal Protocol.

Armstrong's development program for epinephrine-HFA consisted of three single dose pharmacokinetic (PK) trials in healthy volunteers, two single dose, dose-ranging trials in adults with asthma, a 12 week Phase 3 safety and efficacy trial in adults and adolescents with an additional 12 week safety extension, and a 4 week safety and efficacy trial in children aged 4 to 11 years. The Phase 3 trials were placebo controlled, and the adult trial also included an epinephrine-CFC comparator arm. In the first review cycle, the sponsor submitted 4 consumer studies, including 3 label comprehension studies and one behavioral (human factors study) evaluating whether subjects could correctly use the device.

As this product would represent the only MDI product available for OTC use, this application was presented to a joint meeting of the Nonprescription Drugs Advisory Committee (NDAC) and Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting on February 25, 2014. At this meeting, FDA presented concerns regarding the device performance given the relatively high number of device malfunctions and dose indicator errors reported in the clinical program. In response to these concerns, Armstrong submitted additional analyses of device and dose indicator performance, which were reviewed during the first cycle.

On May 22, 2014, FDA took a complete response action due to product quality, nonclinical, and clinical deficiencies. Specifically, the following deficiencies were identified:

- 1) cGMP deficiencies for the active pharmaceutical ingredient (API) manufacturer
- 2) lack of nonclinical qualification of the excipient thymol for chronic use via the oral inhalation route
- 3) lack of assurance that consumers can adequately use the product correctly without the intervention of a health care professional

The usability issue is especially problematic for an OTC product because consumers will be using the device without the oversight of a health care professional who the user might call if there is a problem. Usability is even more concerning considering that this product is

indicated for acute relief of asthma symptoms, which if not treated promptly may result in adverse asthma outcomes, including hospitalization and death.

On December 23, 2016, FDA took a second complete response action because the human factors study failed to demonstrate that consumers could follow the instructions to use the device as directed, with approximately 30% of participants in the human factors study failing at least one of three primary critical use tasks (initial priming of the inhaler, cleaning of the inhaler, and routine use of the inhaler), potentially leading to clinically important under or supra-therapeutic dosing. Manufacturing and toxicology deficiencies were resolved.

This summary review will provide an overview of the complete response to the deficiencies identified during the second cycle and other issues that were addressed during the third cycle review; topics that were fully addressed in the first and second cycle reviews will not be revisited, except as necessary to the discussion of clinical risk benefit.

2 BACKGROUND

2.1 *Asthma*

Asthma is a chronic inflammatory disease of the airways characterized by varying and recurring symptoms of shortness of breath, chest tightness, wheezing and cough, airflow obstruction, bronchial hyper-responsiveness, and underlying inflammation.

The classification of asthma is evolving¹. The NHLBI National Asthma Education and Prevention Program (NAEPP) Guidelines classification of asthma², includes four categories based on the level of symptoms, nighttime awakening from symptoms, SABA bronchodilator use for symptom control, interference with normal activity, and lung function as well as the risk of exacerbations. This classification includes a category of mild intermittent asthma as the mildest form which can be treated with intermittent short-acting beta-agonist bronchodilators on an as needed basis. To establish a diagnosis of asthma, the NAEPP Guidelines state that the clinician should determine that:

- Episodic symptoms of airflow obstruction are present
- Airflow obstruction is at least partially reversible, and
- Alternative diagnoses are excluded

The proposed Drug Facts label for epinephrine-HFA proposes an indication for “mild symptoms of intermittent asthma” which includes patients with intermittent asthma only. In addition, the label contains a “Do not use unless a doctor said you have asthma.” This indication and warning are consistent with the previously marketed epinephrine-CFC product.

¹ Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018. Available from: www.ginasthma.org

² National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication nu. 08-4051). Full text available online: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

2.2 *Relevant regulatory history since the second review cycle*

Since the second review cycle, FDA and Armstrong had the following interactions:

- **March 23, 2017 End of Review Type A meeting**
 - Discussion of FDA's determination that the human factors study failed to demonstrate that consumers could use the product safely and effectively in the OTC setting
 - FDA outlined recommended labeling changes, noting that these would need to be tested with an additional human factors study
- **June 27, 2017 Formal Dispute Resolution Request**
 - Armstrong sought determination that the conducted human factors study is adequate to support approval, citing human factors studies with nasal steroids as examples
- **September 2, 2017: ODEIV denial of Formal Dispute Resolution Request**
 - Dr. Charles Ganley denied the dispute specifically noting that "failure to use an inhaler correctly for the treatment of asthma symptoms can have more serious clinical consequences than incorrectly using a nasal steroid for upper respiratory symptoms."
- **March 2, 2018: FDA Advice letter regarding human factors protocol**
 - Recommendations provided regarding data collection, definitions of task success and failure, and the moderator script to reduce bias
 - Advice noting that whether the CMC bench studies would support the proposed labeling would be a review issue

2.3 *Regulatory history and precedence for development program*

Epinephrine, one of the first sympathomimetic agents in medicine, has been marketed in the United States in a variety of different formulations since 1901, with use in the treatment of asthma dating back to the early 1900s. The first route of administration widely used was intravenous or subcutaneous injection; later, administration by oral inhalation was adopted. Epinephrine in an MDI formulation utilizing CFCs (Primatene[®] Mist) was approved for OTC use for the treatment of symptoms of asthma in 1967 under NDA 16-126 (Wyeth). A generic version was approved under ANDA 87-997 (Armstrong) in 1984. Armstrong subsequently purchased the Primatene Mist trademark for their product, and Wyeth discontinued their product.

In addition to marketing under NDA and ANDA, epinephrine solution for inhalation (using a rubber bulb nebulizer) is generally recognized as safe and effective (GRASE) for marketing without prior FDA approval under the OTC Drug monograph (final rule at 21 CFR 341.16 and 21 CFR 341.76) for Cough, Cold, Allergy, Bronchodilator and Antiasthmatic Drug Products for Over-the-Counter Human Use. The monograph indication and asthma warnings are the same as those proposed for the current application. In 1996, FDA issued a final rule to removed pressurized MDI aerosol container dosage forms for epinephrine from the monograph, citing a need for pre-market review to establish safety and efficacy of the non-CFC formulations and to confirm testing for proper device functioning. In 2014, a joint meeting of the Pulmonary Allergy Drugs Advisory Committee

and the Nonprescription Drugs Advisory Committee voted to remove other formulations of epinephrine (e.g. those administered via a rubber bulb nebulizer) from the OTC drug monograph; however, FDA has not yet published a rulemaking to address the advisory committee recommendations.

CFCs are organic compounds that are broken down by strong ultraviolet light in the stratosphere. CFC breakdown releases chlorine atoms that deplete the ozone layer, resulting in increased levels of ultraviolet-B radiation that may increase cataracts and skin cancer. Beginning in 1996, MDIs using CFC propellants began to be phased out to protect the environment under the Montreal Protocol on Substances that Deplete the Ozone Layer. The process for the phase out of CFC use for epinephrine MDIs began in 2006 with an FDA advisory committee meeting, a proposed rule in 2007, and a public meeting in 2007. In the 2007 proposed rule, FDA proposed an end date (effective date) of December 31, 2010, for the use of CFCs for epinephrine MDIs. In comments on the proposed rule, the manufacturer of epinephrine CFC MDIs requested additional time (December 31, 2011) to reformulate the product. The Final Rule was published in 2008 and based upon a request from the manufacturer, the end date (effective date) for use of CFCs for epinephrine MDIs was December 31, 2011³.

This CFC phase out program occurred for all MDIs with CFC propellants, the majority of which were prescription. Because inhalational products are locally acting in the lung, reformulation requires new clinical dose ranging, safety and efficacy studies to ensure proper dosing; however, a relatively abbreviated drug development program is otherwise recommended. Product labeling changes are generally limited to new clinical data and to those instructions for use necessary for the new inhaler, with indications and warnings remaining the same. Because this product development program was a replacement for a product that was removed from the market for environmental reasons rather than safety or efficacy reasons, the development program relied upon the FDA's prior findings for approval of NDA 16-126. As such, the sponsor was not required to specifically address self-selection issues related to diagnosis of mild symptoms of intermittent asthma or an actual use trial.

This development program for an asthma product is unique in the OTC setting given the long marketing history of the product in the OTC setting, regulatory precedent for labeling of epinephrine, both in an NDA and under the OTC drug monograph, and particular characteristics of the drug (e.g. extremely short acting). It would likely not translate to other OTC asthma products without a similar marketing history.

3 CHEMISTRY, MANUFACTURING, AND CONTROLS

3.1 Active ingredient

The active ingredient, epinephrine, is a phenylethylamine in the class of naturally occurring endogenous hormones and neurotransmitters called catecholamines, which include epinephrine, norepinephrine, and dopamine. Epinephrine is produced by the adrenal

³ Federal Register Volume 73, no 224: 21 CFR Part 2: Use of Ozone-Depleting Substances; Removal of Essential-Use Designation (Epinephrine) Final Rule; Nov 19, 2008.

medulla. It is a non-selective (both alpha and beta) adrenergic receptor agonist that results in the physiologic effects of vasoconstriction, increased peripheral vascular resistance, increased cardiac contractility and heart rate, decreased mediator release, and bronchodilation.

The (b) (4) drug substance is manufactured at a (b) (4) facility in (b) (4). The drug substance is (b) (4). The drug substance produced by (b) (4). The DMF (b) (4) associated with this drug substance was found to be acceptable in the first cycle. Manufacturing and testing facilities associated with the drug substance were re-inspected and found acceptable during the second cycle.

Late in this review cycle, FDA became aware that the drug substance manufacturer, (b) (4), ceased manufacture of epinephrine, raising a potential issue regarding product supply. However, Armstrong has proposed a reasonable approach to address this issue as summarized by Dr. Danae Christodoulou, in the OPQ Branch Chief review:

The drug substance manufacturer, (b) (4) has ceased manufacture of epinephrine as of December 2017, but maintains an active DMF (b) (4) with the FDA and has received acceptable cGMP recommendation in 2016 (see OPQ review #2, dated 12/2/2016 in Panorama). The applicant has procured supplies of epinephrine from (b) (4) for manufacture of drug product (b) (4). In addition, the applicant committed to (b) (4). This provides for an acceptable, viable manufacturing supply chain of the drug product.

A final facilities determination has been made by OPQ for approval of the application, and this issue does not appear to have significant clinical consequences affecting safety or efficacy of the product in light of the sponsor's proposed resolution. Therefore, I agree with the overall recommendation by OPQ for approval with a post-marketing commitment to submit a supplement for an alternative drug substance manufacturer.

3.2 Epinephrine HFA MDI and device performance

The epinephrine HFA MDI includes a 14 ml anodized aluminum canister with (b) (4) metering valve (Model (b) (4) 50 µl metering (b) (4), a top mounted dose indicator (b) (4) Part No. (b) (4), and an orange L-shaped actuator (b) (4) with a red dust cap (see Figure 1). The canister contains a (b) (4) suspension of epinephrine in propellant HFA-134a, ethanol, thymol (b) (4) and polysorbate 80 (b) (4). Thymol is not found in other currently marketed inhalational products, but was adequately qualified for use in this product (see second cycle review, nonclinical). Each epinephrine HFA MDI contains 160 metered sprays releasing 125 mcg of epinephrine per actuation.

Figure 1: Epinephrine HFA MDI



The proposed dose is one or two inhalations with instructions to wait at least 4 hours between doses, with a maximum of 8 inhalations per 24 hour period. The product is a standard press-and-breathe MDI that comes assembled. Given the significant issues with patient reports of device and dose indicator performance identified in the clinical trials, two independent CMC reviews of device and dose indicator were conducted during the first cycle review. Reviewers with particular expertise in MDI drug products were included in both reviews. The reviews independently concluded that the device and dose counter function acceptably when used exactly as labeled. However, failure to follow the instructions for cleaning, drying, dosing, and priming and instructions regarding dropping may result in a variety of different device performance issues including dispensing of a variable dose, device clogging, and dose indicator miscounting.

FDA requires an evaluation of product performance for all new MDI asthma products. Such an evaluation typically includes in vitro assessment of ruggedness and reliability, root-cause evaluation of all device complaints, and testing of a random sampling of clinical trial device units. Any device malfunctions seen in clinical trials are of concern, particularly for an asthma reliever medication, which may be used in a life-saving rescue situation.

Based on the original submission, of the 3508 MDIs that were returned during the Phase 3 trials, patients or study sites reported a malfunction with 251 (7.2%) of them. It is unusual to have 7% of devices reported as malfunctioning during a clinical trial. Clinical trials are generally considered to be a best-case-scenario for device performance because patients receive detailed instructions for use and follow up. While the sponsor's root cause analysis of these errors did not identify a specific device defect, the high numbers of reports suggested that consumers would have difficulty using the proposed product correctly as labeled in the clinical trial. Similarly, although the device and dose counter function acceptably when used exactly as labeled, simulation testing demonstrates that failure to follow the instructions may result in clinically significant performance issues. The complexity of steps required for shaking, priming, actuation, and cleaning may contribute to usability issues.

In order to address this usability concern, Armstrong submitted additional device testing data during the second and third cycles that were used to inform labeling changes and

further consumer human factors testing. These device testing results are also informative in interpreting the clinical importance of the results of consumer testing. Consumer errors in following labeled instructions that result in meaningful changes to the delivered dose are more critical than those that do not.

Based on the results of bench testing, three tasks were determined to be critical for the user to perform to ensure proper dosing: priming, cleaning, and routine use (dosing). If these tasks are not performed correctly, the consumer will not reliably receive the correct dose. Therefore, the human factors studies focused on these three tasks. Based on the results of bench testing from all three cycles, the chemistry team concluded that the following conservative instructions for use are supported:

- Prime: shake and spray 4 times before first use
- Cleaning frequency: clean each day after use
- Dosing: shake and spray one time before each inhalation

Although the totality of the device bench testing data support a cleaning frequency of every 3 days of use, this task frequency is known to be difficult for consumers to remember. Performing a task daily is both more conservative and more likely to be remembered, which is why the clinical and labeling teams recommended daily cleaning.

4 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

All nonclinical issues relating to excipients were satisfactorily resolved in the second cycle, and no additional toxicology data were submitted during this cycle review.

5 SAFETY

The pharmacologic and physiologic effects of epinephrine are well characterized, including stimulation of the sympathetic nervous system to increase heart rate and the force of heart contractions, increase blood pressure, and increase the breakdown of glycogen into glucose resulting in increased blood glucose levels. The β_2 effects of epinephrine include relaxation of bronchial smooth muscles resulting in an increase in bronchial airflow, dilation of blood vessels in skeletal muscles and the liver, release of glucose into the circulation, and inhibition of release of mediators from stimulated eosinophils, mast cells, and basophils. Safety data for epinephrine-HFA was reviewed in light of these known effects of the active moiety.

5.1 Safety in clinical trials

Safety in clinical trials and cardiac safety was reviewed during the first cycle and deemed to be acceptable for approval. The safety profile in the adult Phase 3 trials does not suggest a serious safety signal, although the clinical trial database is small, with 373 adult and adolescent subjects and patients exposed to any dose of epinephrine-HFA. Of these, 248 received more than one dose of drug. In addition, 35 pediatric patients aged 4-11 received more than one dose of epinephrine-HFA.

The most commonly reported adverse event was tremor, which was the one event with a notable imbalance, occurring in 10% of patients in the epinephrine-HFA group compared to

2% in the placebo and epinephrine-CFC groups. This finding is consistent with the non-selective beta-agonist effect of the drug. Other events occurring more frequently in the epinephrine-HFA group compared to control groups were throat irritation, cough, feeling jittery, bronchitis, dizziness, respiratory tract irritation, glossodynia, ligament sprain, and muscle strain.

The high dose PK study in healthy volunteers demonstrated substantial increases in blood pressure (>50 mmHg systolic) and pulse (>60 bpm) in some patients 10 minutes after a single dose of 1250 mcg and 1600 mcg, although the median increases were more modest (pulse increase of 5-6 beats, systolic blood pressure increase of 9-14 mmHg, diastolic blood pressure increase of 1-3 mmHg). To achieve a dose of 1250 mcg, a patient would have to take 10 inhalations of the proposed 125 mcg dose in rapid succession; a dose of 1600 mcg would require 12-13 inhalations. No such changes were observed at the proposed maximal dose of 250 mcg, giving some idea of the safety margin available in the case of overdose. This information is particularly relevant for the application, since failure to shake the device would result in a superpotent dose per spray, up to approximately twice the labeled dose (i.e. a maximal dose of 250 mcg per spray).

5.2 Consumer studies

First cycle

In the first cycle, Armstrong conducted 4 consumer studies, including 3 label comprehension studies and one behavioral (human factors study) evaluating whether subjects could correctly use the device. Given the long history of use of epinephrine CFC, the development program for epinephrine HFA was designed to focus only on elements that differed from the CFC product label, and did not focus on self-selection or safety questions related to the label that are commonly evaluated as part of a de novo OTC program.

The label comprehension studies were iterative and focused on 3 primary communication objectives, all related to the dose indicator. In addition, the label comprehension studies identified limitations in consumers' understanding of the following critical information: the need to prime the inhaler before using the first time, the need to clean the product daily after use, and the need to reprime when wet.

The first cycle human factors study had a number of methodological issues. However, suboptimal performance in several key areas that could impact device performance were noted, with only 74% of subjects shaking the MDI prior to priming, 82% priming prior to use, 64% correctly washing the mouthpiece through the top opening, and 74% shaking the MDI prior to use. Some consumers had difficulty removing the canister to clean the product, and the study did not assess whether consumers correctly reassembled the product after cleaning. Incorrectly completing these steps could cause dose variability and clogging with resulting failure to deliver the appropriate dose, a potential issue for both safety and efficacy.

Second cycle label comprehension studies

In the second cycle, Armstrong conducted three additional label comprehension studies followed by a human factors study. Label comprehension studies were iterative and focused on optimizing understanding of cleaning, priming, placing finger in the center of the dose

indicator to spray, and not to rely on the dose indicator if the product is dropped. Overall, these results demonstrated that consumers continued to demonstrate less than optimal comprehension for priming objectives, particularly in the low literacy population (lower bound of the confidence interval 66-77% answering correctly depending on the question). Former Primatene CFC users generally scored more poorly than non-Primatene users. Based on these results, Armstrong substantively simplified instructions for use and added additional diagrams. For example, the priming instructions were modified from (b) (4)

Rather than retesting the newly modified label in further label comprehension studies, the sponsor moved on to a human factors study with the revised label. This approach is reasonable given that the major elements being tested were related to instructions for use.

Based on feedback from the Advisory Committee, Armstrong also assessed label comprehension of three safety warnings: 1) “Children under age 12, do not use”, 2) “Do not use more than 8 inhalations in 24 hours,” and 3) “See your doctor if you have more than two asthma attacks in one week.” Results showed good comprehension in both normal and low literacy populations of “Children under age 12, do not use” and “See your doctor if you have more than two asthma attacks in one week”, with 97% and 98% of the overall population answering correctly. “Do not use more than 8 inhalations in 24 hours” scored less well, with 92% [95% CI (89%, 94%)] of the overall population and 89% [95% CI (82%, 94%)] of the low literacy population answering correctly. Of note, this warning is worded more conservatively than the monograph warning, which permits up to 9 doses in a 24 hour period, so was deemed acceptable by the social science and clinical teams.

Second cycle human factors study

Because the drug facts label (DFL) and consumer instructions for use (consumer information leaflet, CIL) were changed substantially subsequent to the final label comprehension study, the human factors study is much more relevant to the overall expected use of the product by consumers. The second cycle human factors study was conducted at two different U.S. testing facilities in 151 adult and adolescent subjects aged 12 to 17 years. Overall, the population included 133 adults and 18 adolescents, of whom 22 (19 adults and 3 adolescents) were low literacy. Thirty-two adult and 7 adolescent subjects had previously used inhalers. Subjects performed 3 simulated-use tasks, and then responded to open-ended questions to assess three label comprehension elements related to understanding the dose indicator. The three primary endpoints evaluated the simulated use tasks of 1) initial priming of the inhaler to prepare it for use, 2) cleaning the inhaler, and 3) routine use of the inhaler. For the primary endpoints in the sponsor’s analyses, subjects were scored as *Completed*, *Completed with Issues*, or *Not Completed*. *Completed with Issues* was defined as subjects who struggled initially to perform the task but self-corrected during the study or performed the task in a way that deviated from the instructions. Subjects were also scored as *Completed with Issues* if they completed the task successfully after being referred to the instructions by the study moderator. In these cases, the moderator would ask the participant if he/she had performed the task in a way that differed from the instructions, which is not an acceptable way to mitigate user errors. Secondary label comprehension endpoints evaluated how to interpret the dose indicator, not relying on the

dose indicator if dropped, and understanding correct finger positioning to ensure the device delivers medication properly with each spray.

Based on FDA's mitigation analysis of the data in this study, approximately 30% of participants in the HF study failed at least one of the three primary tasks (critical use tasks) of the study: initial priming of the inhaler (Task 1), cleaning of the inhaler (Task 2), or routine use (re-priming) of the inhaler (Task 3). FDA's analysis for Task 1, Task 2 and Task 3 found 13%, 12%, and 13% of participants had errors that could lead to clinically important under or supra-therapeutic dosing. Because some participants had clinically important errors in more than one task, this yields 30% of participants with an error for at least one task. This is an important clinical concern because, if these tasks are not correctly performed, users of this product will not reliably receive the correct dose and may either under-dose, which will likely result in lack of efficacy, or receive a supra-therapeutic dose. If users do not obtain relief with the inhaler they will view the product as ineffective.

The secondary label comprehension objectives for the dose indicator and finger positioning tested well. Only a small number of subjects failed to understand the dose indicator (2/151) or the potential for malfunction if dropped (4/151). Encouragingly, all 151 participants understood correct finger positioning and how to hold the inhaler correctly. This was initially raised as a potential concern because failure to hold the inhaler upright could result in discharge of propellant only and eventual failure to deliver a dose.

In considering the implications of the failures observed during human factors testing, it is important to understand that the human factors study represents a best case scenario because subjects were observed under conditions of low stress and were supplied with both the packaging (including the DFL) and the CIL. Consumers actually using the inhaler may or may not have the instructions for use immediately available. Further, since the product is used as a rescue inhaler for intermittent asthma, consumers will likely be experiencing dyspnea and some degree of respiratory distress at the time of use, which may preclude substantial time to read and comprehend labeling. Based on the results of this testing, the sponsor further modified the label to improve comprehension, including making key instructions with pictograms very visible directly on the device.

Third cycle human factors study

Based on the results of consumer testing (label comprehension and human factors) in the second cycle, Armstrong modified the labeling further to add instructions for use and pictograms to the inhaler itself, simplifying instructions for use and limiting to one page, and updating the instructions based on what is supported by the CMC bench studies. The human factors study was conducted in 30 adults and 15 adolescents with asthma with and without inhaler experience. A total of 40% of the adults and 67% of the adolescents were low literacy. The study focused on the three steps determined to be most critical in ensuring proper dose delivery:

- Activating before first use: Shake and spray into the air; repeat 4 times
- Routine use (dosing): Shake and spray into the air one time before inhalation
- Washing: Wash after each day of use

Results of the study demonstrated three use errors for activating, two use errors for dosing, and one use error for washing. The two use errors for dosing were determined to be an artifact of the artificial setting of the study, while the other errors primarily occurred because of prior inhaler experience leading to failure to read the directions. The Division of Medication Errors and Prevention (DMEPA) determined that these use errors likely could not be improved with revisions in labeling or other modifications to the user interface. Given the conservative approach to the instructions and the type of errors observed, consumers would be likely to get some benefit from use of the product even if instructions are not followed perfectly, especially given the option to take a second dose if there is no relief with the first dose. Therefore, the consensus of reviewers from DMEPA, clinical and social science, was that the human factors study demonstrated adequate support for approval. I concur with this recommendation.

5.3 *Differences between epinephrine-HFA and Primatene Mist®*

Apart from the obvious differences in propellant and inhaler design, a number of differences exist between the epinephrine-HFA and the previously-marketed epinephrine-CFC product. It is likely that consumers who previously used and are familiar with the CFC product will also use the epinephrine-HFA product. As such, it is possible that confusion may occur for patients purchasing the product in the OTC setting without assistance of a healthcare intermediary. These differences were described in my first cycle review; however, I reiterate them here because it is important to understand that compared to CFC versions HFA inhalers require much more diligent adherence to labeled instructions in order to obtain the correct dose. Consumers may also be familiar with various dry powder inhalers (DPIs) on the market, which have very different labeled instructions for use.

- The formulation for epinephrine-HFA is a suspension rather than a solution as for the CFC product. As such, the MDI must be shaken prior to use to prevent settling. If the MDI is not shaken, this could potentially result in dose variability leading to higher doses administered.
- Epinephrine-HFA must be cleaned daily to prevent clogging. In contrast, because CFC propellants also function as cleaning agents, daily cleaning was not required for epinephrine-CFC.
- Epinephrine-HFA must be primed prior to each use. Priming was not required for epinephrine-CFC.
- Epinephrine-HFA contains a dose counter whereas the epinephrine-CFC product had a transparent glass reservoir allowing patients to visually determine when the drug solution was running out.
- The proposed population for epinephrine-HFA is adults and adolescents age 12 and older, while the CFC product was approved down to age 4.
- Pharmacokinetic studies demonstrate that there are greater systemic blood levels with epinephrine-HFA compared to epinephrine-CFC. In particular, the C_{max} is 4.5 times higher.

- The dosing instructions for epinephrine-HFA are different from the CFC product. The proposed dosing for epinephrine-HFA is one to two inhalations per dose not more often than every 4 hours, and not to exceed 8 inhalations in 24 hours. Dosing for epinephrine-CFC was one or two inhalations every 3 hours with no maximum.
- The sponsor notes the following advantages of epinephrine-HFA compared to the CFC product: 1) elimination of the CFC propellant to meet the requirements of the Montreal Protocol, 2) proposed dose is reduced by 43% with similar efficacy, 3) the pH of the new formulation is neutral rather than acidic, 4) amount of alcohol in the formulation (b) (4) which can reduce false positive Breathalyzer tests, and 5) an aluminum canister replaces the glass bottle.

5.4 *Safety conclusions*

The sponsor has taken a number of steps during this review cycle to improve and simplify labeling and instructions for use. Armstrong also conducted robust device testing to identify the clinical implications of various use errors, using this data to take a conservative approach to labeling. Given that device failures related to use errors are also reported with prescription HFA inhalers, it seems unlikely that any labeling changes will be able to result in perfect adherence to labeled instructions. The repeat human factors study conducted during the third cycle demonstrated that users were generally able to complete the three critical steps to ensure proper dosing, suggesting that the product is likely to function as intended in the hands of consumers.

Other important safety issues considered for this application were cardiac safety, adverse asthma outcomes, and misuse and abuse contributing to cardiac and respiratory adverse events. Because epinephrine is a non-selective beta-agonist, it is expected to have dose dependent sympathetic effects, including elevations in blood pressure and heart rate. To address this issue, Armstrong submitted two separate dose ranging studies to ensure that the lowest dose providing consistent effectiveness was selected. In addition, the high dose PK study in healthy volunteers demonstrated that increases in heart rate and blood pressure did not occur until doses of 1250 mcg (5 times the highest recommended dose) were reached, suggesting that consumers would need to use much more than the highest recommended dose to get these effects. The short duration of action of epinephrine compared to prescription beta-agonists limit potential risks related to unopposed sympathomimetic effects and asthma-related deaths observed with high-dose, long-acting beta-agonists. The label instructs consumers to “ask a doctor before use if you have ever been hospitalized for asthma, or have heart disease or high blood pressure,” among other warnings.

Post-marketing safety reports for epinephrine CFC were evaluated for a 15 year period (1997-2012), including specific consideration of cardiac adverse events, asthma-related adverse events and events related to misuse. During this time period, there were 116 serious adverse events reported, including 41 deaths. Given limited information and various confounding factors, causality could not clearly be determined for these deaths. Twelve deaths included cardiac-related AEs, and 5 were related to abuse/misuse of the products. There were two deaths reported in children, one in a 10 year old boy who seized while in a pool, and one in a 17 year old female who died of an asthma exacerbation. The sponsor

reports that there were 66 million unions of Primatene distributed during this time period. Given the limitations of post-marketing reporting, these events do not suggest a particular safety issue related to use of the CFC product.

Misuse of epinephrine HFA involves consumers using more than recommended on the product label in order to obtain symptom relief instead of seeking medical care. The obvious concern is that this could lead both to adverse asthma outcomes from failure to obtain appropriate escalation of therapy and tachyphylaxis to the beta-agonist effects with resultant asthma-related death, a known potential outcome of high dose beta-agonists. While this is a concern with any beta-agonist, the concern is heightened for an OTC product because therapy is not occurring under the supervision of a health care professional. Because inhalers containing large numbers of doses or packaging of multiple inhalers together could potentially encourage consumers to use the product daily and delay health care provider visits, we are limiting package size of epinephrine HFA to immediate containers containing 160 metered sprays or fewer, with no more than one inhaler packaged and sold together, consistent with its intended use as a rescue medicine for occasional mild asthma symptoms. An inhaler containing 160 metered sprays provides approximately 10 days of dosing at the maximum amount recommended in the product label. This recommendation is consistent with advice of the advisory committee.

6 ADVISORY COMMITTEE MEETING

During the first review cycle, the application was discussed during a joint meeting of the Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee. The majority of the committee did not agree that the risk/benefit profile of epinephrine inhalation aerosol 125 mcg per actuation supported OTC use for the temporary relief of mild symptoms of intermittent asthma. The vote was 6 yes, 18 no, and 1 member did not vote. Committee members voted “No” primarily due to safety concerns, including: a lack of long-term safety data, limited data on use by adolescents 12-18 years of age, the device and dose indicator have issues that could impact safe use, consumers’ inability to adequately assess the severity of their asthma, the need for a learned intermediary to adequately educate asthma patients about their diagnosis, and national guidelines recommending against use of epinephrine for the treatment of asthma. Of note, several advisory committee members were concerned that the high number of actuations per inhaler could encourage chronic use and delay health care provider visits.

Since there were no new issues, the application was not discussed in an advisory committee meeting during the second or third review cycle.

7 PEDIATRICS

The previously marketed epinephrine CFC formulation was approved down to age 4 years. Pediatric patients aged 12 and above were included in the adult asthma trials using the HFA formulation performed to support efficacy and safety of this application. A 4 week efficacy trial in pediatric patients aged 4-11 years was conducted, but was underpowered and failed to demonstrate statistically significant efficacy. As such, Armstrong is not currently seeking an indication in children aged 4-11 years. Labeling will include a specific contraindication to use in children younger than age 12 with the following language:

- Children under 12 years of age: do not use; it is not known if the drug works or is safe in children under 12

The Pediatric Review Committee (PeRC) agreed to a waiver for children under age 4 years and deferral of studies in children aged 4 to 11 years, which will include a single trial to evaluate safety, efficacy and PK. This study will be conducted as a post-marketing requirement under PREA with final submission of the study report by August 2020.

8 LABELING

8.1 *Proprietary name*

The sponsor proposed the proprietary names (b) (4) (December 12, 2013) and (b) (4) (April 16, 2014). Members of the Advisory Committee raised the concern that a proprietary name using the same root name Primatene as the CFC formulation, known as Primatene Mist, could lead to consumer confusion and increase user error with the device due to the large number of differences between the products. This concern was echoed by the social science and clinical OTC teams during the first review cycle. During the second cycle review, (b) (4)

The name Primatene Mist was once again submitted. Due to the length of time that the CFC inhaler has been off the market (7 years), the issue with confusion was considered to be less relevant, so the name Primatene Mist was found acceptable.

8.2 *Consumer labeling*

Given the Complete Response Action, a full labeling review was not conducted during the first review cycle. During this second cycle, a complete labeling review was performed by the interdisciplinary science team, with input from DMEPA, the clinical team, the CMC team, and the social science team. A number of recommendations were conveyed to the sponsor, primarily related to Drug Facts specifications and consistency of language throughout the principal display panel on the outer carton, the DFL on the outer carton, the abbreviated DFL on the metal canister, and the CIL. Armstrong agreed to these changes, which were tested in the human factors study, reviewed this cycle.

During this review cycle, the review team completed another complete labeling review, taking into account key information from both the chemistry reviews and the human factors reviews. The DFL and CIL include a reference to a website, which contains information about asthma in general, the epinephrine HFA product, and several videos on how to use the product. The labeling team also reviewed the website and had several suggestions about content and consistency. One unique element of labeling for this product, which was tested in the human factors study, was inclusion of key use steps with accompanying color pictograms, in easily readable text on the actuator itself. See Figure 2. Because the user may not have immediate access to the DFL or CIL when the inhaler is being used, emphasizing proper use instructions on the actuator may have significant benefit in reminding consumers of key use steps.



Figure 2: Actuator label

In this cycle, the sponsor proposed eliminating [REDACTED] (b) (4). However, the CMC team determined that the bench data of simulated use provided in this cycle and previous cycles did not support these changes due to high dose variability. As such, labeling (including the online videos) was revised to read shake then spray into the air one time prior to each inhalation and wash after each day of use. These changes were not determined to be sufficiently substantive as to require performing additional consumer testing (human factors study) of the revised instructions for use.

9 DECISION/ACTION/BENEFIT RISK ASSESSMENT

9.1 Regulatory action

Armstrong has submitted adequate data to support approval of epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA), at a dose of 125 mcg/actuation for over the counter (OTC) use for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. Two of the three deficiencies raised in the first cycle review were resolved during the second cycle. Subsequently, Armstrong has redesigned the label, including providing prominent instructions for the most important key steps in dosing right on the device actuator. In addition, the sponsor provided additional in vitro CMC testing to support instructions for use. The human factors study using the revised labeling submitted during this cycle adequately demonstrated that consumers can follow instructions for use, resolving the third deficiency.

9.2 Risk Benefit assessment

Epinephrine HFA is a short-acting bronchodilator for the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of the chest, and shortness of breath. OTC availability may provide benefit to consumers due to increased access to a short-acting rescue medication without requiring a prescription. For consumers with mild, intermittent asthma, being able to purchase a rescue inhaler in the OTC setting could supplement prescription medication for cases in which a prescription had run out or was unavailable. Efficacy and safety of the 125 mcg HFA product was demonstrated in asthma patients in a 12 week study with an additional 12 weeks of safety follow up. As expected,

tachyphylaxis did occur in this trial after 12 weeks of continuous use, supporting the recommended as needed, intermittent dosing.

Key risks of epinephrine HFA include consumers not getting accurate dosing (or failure to receive a dose) due to use errors with the inhaler, cardiac safety, adverse asthma outcomes, and misuse and abuse contributing to cardiac and respiratory adverse events. While it will likely not be possible to completely eliminate use errors, at this point, I believe that labeling has been sufficiently optimized that consumers will be able to follow the instructions for use of the inhaler to obtain the correct delivered dose, and further optimization is unlikely to result in improvement. The dose of 125 mcg was chosen based on results of two dose ranging studies to deliver the lowest dose providing reliable efficacy to minimize adverse effects, and package size will be limited to a single inhaler with a maximum of 160 metered actuations (total of approximately 10 days of maximal use) to minimize overuse. A high dose PK study in healthy volunteers delineated the dose-related cardiac effects, suggesting that consumers would likely need to take about 5 times the maximum labeled dose at one time to get clinically important elevations, which is an adequate safety margin. In addition, the label includes a prominent asthma alert warning, a contraindication to use unless a doctor said you have asthma, and instructions to ask a doctor before use if you have ever been hospitalized for asthma, have heart disease, high blood pressure, or are taking prescription drugs for asthma, among other warnings.

The very long OTC marketing history and known adverse event profile of the CFC version of this product are supportive of the safety profile of the HFA product for OTC use. Taking these factors into account, the overall risk-benefit assessment supports OTC approval of epinephrine HFA for the temporary relief of mild symptoms of intermittent asthma for adults and children 12 years of age and older.

9.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

9.4 Recommendation for other Postmarketing Requirements and Commitments

This application is being approved with a post-marketing requirement under PREA for a multiple dose safety and efficacy study in children aged 4 to 11 years with asthma. The study must also include an assessment of pharmacokinetics. Armstrong agreed to the following timelines for submission:

- Final protocol submission: February 2019
- Study completion: May 2020
- Final report submission: August 2020

Because the API manufacturer has discontinued production of epinephrine, Armstrong has also agreed to a post-marketing commitment to (b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THERESA M MICHELE
11/07/2018

Summary Review for Regulatory Action

Date	December 23, 2016
From	Theresa M. Michele, MD Director, Division of Nonprescription Drug Products
Subject	Division Director Summary Review
NDA/BLA #	205920 SD-39
Applicant Name	Armstrong Pharmaceuticals, Inc.
Date of Submission	June 28, 2016 (Class 2 Resubmission)
PDUFA Goal Date	December 28, 2016
Proprietary Name / Established (USAN) Name	Primatene Mist (epinephrine inhalation aerosol)
Dosage Forms / Route of Administration / Strength	Aerosol, metered / Inhalation / 125 mcg/actuation
Proposed Indication(s)	Temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older
Regulatory Action	Complete Response

1 INTRODUCTION

This supplement is a complete response to deficiencies identified during the first cycle for the 505(b)(2) application for NDA 205,920. In this application, Armstrong Pharmaceuticals, Inc. (Armstrong) is seeking approval for epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA), at a dose of 125 mcg/actuation for over the counter (OTC) use for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older.

Epinephrine-HFA is a short-acting beta₂-agonist (SABA) bronchodilator used as a quick relief medication for acute bronchospasm. Armstrong is positioning the epinephrine-HFA MDI (metered dose inhaler) as an alternative to the previously marketed Primatene[®] Mist epinephrine MDI, which was removed from the market in 2011 due to the phase out of ozone-depleting chlorofluorocarbon (CFC) propellants under the Montreal Protocol.

Armstrong's development program for epinephrine-HFA consisted of three single dose pharmacokinetic (PK) trials in healthy volunteers, two single dose, dose-ranging trials in adults with asthma, a 12 week Phase 3 safety and efficacy trial in adults and adolescents with an additional 12 week safety extension, and a 4 week safety and efficacy trial in children aged 4 to 11 years. The Phase 3 trials were placebo controlled, and the adult trial also included an epinephrine-CFC comparator arm. In the first review cycle, the sponsor submitted 4 consumer studies, including 3 label comprehension studies and one behavioral (human factors study) evaluating whether subjects could correctly use the device.

As this product would represent the only MDI product available for OTC use, this application was presented to a joint meeting of the Nonprescription Drugs Advisory Committee (NDAC) and Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting on February 25, 2014. At this meeting, FDA presented concerns regarding the device performance given the relatively high number of device malfunctions and dose indicator errors reported in the clinical program. In response to these concerns, Armstrong submitted additional analyses of device and dose indicator performance, which were reviewed during the first cycle.

On May 22, 2014, FDA took a complete response action due to product quality, nonclinical, and clinical deficiencies. Specifically, the following deficiencies were identified:

- 1) cGMP deficiencies for the active pharmaceutical ingredient (API) manufacturer
- 2) lack of nonclinical qualification of the excipient thymol for chronic use via the oral inhalation route
- 3) lack of assurance that consumers can adequately use the product correctly without the intervention of a health care professional

The usability issue is especially problematic for an OTC product because consumers will be using the device without the oversight of a health care professional who the user might call if there is a problem. Usability is even more concerning considering that this product is indicated for acute relief of asthma symptoms, which if not treated promptly may result in adverse asthma outcomes, including hospitalization and death.

This summary review will provide an overview of the complete response to these deficiencies and other issues that were addressed during the second cycle review; topics that were fully addressed in the first cycle review will not be revisited.

2 BACKGROUND

2.1 Asthma

The proposed Drug Facts label for epinephrine-HFA proposes an indication for “mild symptoms of intermittent asthma” which includes patients with intermittent asthma only. In addition, the label contains a “Do not use unless a doctor said you have asthma.” This indication and warning are consistent with the previously marketed epinephrine-CFC product.

2.2 Relevant regulatory history since the first review cycle

Since the first review cycle, FDA and Armstrong had the following interactions:

- **October 1, 2014 End of Review Type A meeting**
 - Discussion of proposed qualification program for the excipient thymol
 - Recommendation to submit the results of the label comprehension and human factors studies for review and request a meeting to discuss study findings and the need for an actual use trial

○ **January 22, 2016 FDA advice letter**

- Feedback provided that protocol design for the human factors trial appears adequate
- Recommendations regarding sampling times, negative control group, and toxicokinetic measurements for the nonclinical study

3 CHEMISTRY, MANUFACTURING, AND CONTROLS

3.1 Active ingredient

The active ingredient, epinephrine, is a phenylethylamine in the class of naturally occurring endogenous hormones and neurotransmitters called catecholamines, which include epinephrine, norepinephrine, and dopamine. Epinephrine is produced by the adrenal medulla. It is a non-selective (both alpha and beta) adrenergic receptor agonist that results in the physiologic effects of vasoconstriction, increased peripheral vascular resistance, increased cardiac contractility and heart rate, decreased mediator release, and bronchodilation.

The (b) (4) drug substance is manufactured at (b) (4) facility in (b) (4). The drug substance is (b) (4). The drug substance produced by (b) (4).

All DMFs associated with this drug substance were found to be acceptable in the first cycle. Manufacturing and testing facilities associated with the drug substance have been re-inspected and found acceptable. This action resolves the CR deficiency for CMC.

3.2 Epinephrine HFA MDI and device performance

The epinephrine HFA MDI includes a 14 ml anodized aluminum canister with (b) (4) metering valve (Model (b) (4) 50 µl metering (b) (4)), a top mounted dose indicator (b) (4) Part No. (b) (4), and an orange L-shaped actuator (b) (4) with a red dust cap (see Figure 1). The canister contains a (b) (4) suspension of epinephrine in propellant HFA-134a, ethanol, thymol (b) (4) and polysorbate 80 (b) (4). Thymol is not found in other currently marketed inhalational products. Each epinephrine HFA MDI contains 160 metered sprays releasing 125 mcg of epinephrine per actuation.

Figure 1: Epinephrine HFA MDI



The proposed dose is one or two inhalations with instructions to wait at least 4 hours between doses, with a maximum of 8 inhalations per 24 hour period. The product is a standard press-and-breathe MDI that comes assembled. In the first cycle, instructions for use of the device stated that it must first be shaken and primed. First cycle instructions stated that it must also be primed if not used for more than 2 days, if it is still wet after cleaning, or if it is dropped. In addition, the inhaler must be shaken immediately prior to dosing. The instructions also require cleaning by disassembling the device and washing with warm water on a daily basis. According to the sponsor, holding the inhaler with the dose indicator up during actuation is important because otherwise it could cause only the propellant to be discharged. If this process were continued over the life of the product, the propellant may be completely discharged and the inhaler would fail to provide any medication.

The epinephrine HFA MDI includes a top mounted dose actuation indicator. This device attaches to the end of the drug product canister using an adhesive label. The dose indicator mechanically counts each actuation. The display advances every 10 actuations and is labeled numerically in increments of 20. When 20 or fewer actuations remain, the display begins to turn red in color. The red zone continues to fill the display until the counter indexes to zero. At this point the display is at the zero count and completely red, indicating the need to replace the inhaler. After the zero count has been reached, additional actuations of the MDI no longer advance the display. The package instructions note that a finger must be placed on the center of the dose indicator during actuation. Instructions also note that if the MDI is dropped, the dose indicator is no longer reliable and patients must keep track of the number of sprays taken.

Given the significant issues with patient reports of device and dose indicator performance identified in the clinical trials, two independent CMC reviews of device and dose indicator were conducted during the first cycle review. Reviewers with particular expertise in MDI drug products were included in both reviews. The reviews independently concluded that the device and dose counter function acceptably when used exactly as labeled and that the labeled instructions for use are supported by simulation data. However, failure to follow the

instructions for daily cleaning, drying, and priming and instructions regarding dropping may result in a variety of different device performance issues including dispensing of a variable dose, device clogging, and dose indicator miscounting.

3.3 Device performance

Background

FDA views an inhalation aerosol product such as the proposed epinephrine HFA to be the sum of its parts, i.e., the product entails all of the device components, the formulation, and any necessary protective packaging. In general, dose delivery is influenced not only by the device components but also by the formulation and any interactions between the formulation and the device components. Even if various device components and formulations have been found to be acceptable in other products, the same performance characteristics cannot be guaranteed for new combinations in new products. Therefore, the Agency requires an evaluation of product performance for all new MDI asthma products. Such an evaluation typically includes in vitro assessment of ruggedness and reliability, root-cause evaluation of all device complaints, and testing of a random sampling of clinical trial device units. Any device malfunctions seen in clinical trials are of concern, particularly for an asthma reliever medication, which may be used in a life-saving rescue situation.

Likewise, while dose indicators are considered a favorable addition to an MDI product, the Agency expects a demonstration of reliability and accuracy in the clinical program. In general, dose indicators are expected to have reliability as close to 100% as possible, especially with regards to undercounting.¹ If a dose counter/indicator undercounts, the indicator will overestimate the number of remaining actuations. This is especially concerning for quick relief medications, such as epinephrine-HFA, in which the dose indicator may incorrectly show that there are remaining doses of medication and a patient fails to get relief of acute bronchospasm. Undercounting of dose counters/indicator for quick relief medications poses a safety concern. In contrast, overcounting is unlikely to result in lack of efficacy, but may pose an issue for patients if they are required to purchase a new MDI despite available doses.

Armstrong evaluated device performance in the Phase 3 trials. Dose indicator performance for the epinephrine-HFA and placebo arms was evaluated separately in the adult trial and safety extension, and Armstrong did not categorize dose indicator errors as a device performance issue. During the trials, patients recorded study drug use, mouthpiece cleaning, and device malfunctions in a diary. All used and unused study drug was collected during site visits, and patients were also queried regarding device malfunctions. Specific manufacturing performance evaluation tests were to be performed on all devices for which there was a malfunction reported as well as a random sample of returned MDI units. In addition, the incidence of overcounting and undercounting for the MDI dose indicators were evaluated and Armstrong revised the component specifications used for accepting the dose indicator.

¹ FDA Guidance for Industry: Integration of Dose-Counting Mechanisms into MDI Drug Products, March 2003.

Device performance

Based on the original submission, of the 3508 MDIs that were returned during the Phase 3 trials, patients or study sites reported a malfunction with 251 (7.2%) of them. See Table 1. Of the 251 MDIs with reports of malfunction, 53 were due to clogging and 31 were not dispensing properly; specifics of the other 167 reports were not provided. Per the original submission, Armstrong stated that 243 of the devices that were reported to malfunction were within specifications, concluding that the reports were erroneous. Of the other 8 devices, one had a broken valve stem, but had been used to dispense some doses prior to breakage, and the other 7 had dose indicators that were damaged or were at zero, precluding testing.

Table 1: MDI device malfunctions reported in the Phase 3 trials (original NDA submission)

Trial	Number of used MDIs returned	Number of MDIs with reported malfunction n (%)
C (adult)	2232	116 (5.2%)
C2 (adult safety extension)	1071	109 (10.2%)
D (pediatric)	205	26 (12.7%)
Total	3508	251 (7.2%)

Source: eCTD Section 3.2.P.2.2; Performance Evaluation Report QARD-018-11-02 FR

It is unusual to have 7% of devices reported as malfunctioning during a clinical trial. Clinical trials are generally considered to be a best-case-scenario for device performance because patients receive detailed instructions for use and follow up. While the sponsor's root cause analysis of these errors did not identify a specific device defect, the high numbers of reports suggests that consumers may have difficulty using the proposed product correctly. Similarly, although the device and dose counter function acceptably when used exactly as labeled, simulation testing demonstrates that failure to follow the instructions may result in clinically significant performance issues. The complexity of steps required for shaking, priming, actuation, and cleaning may contribute to usability issues.

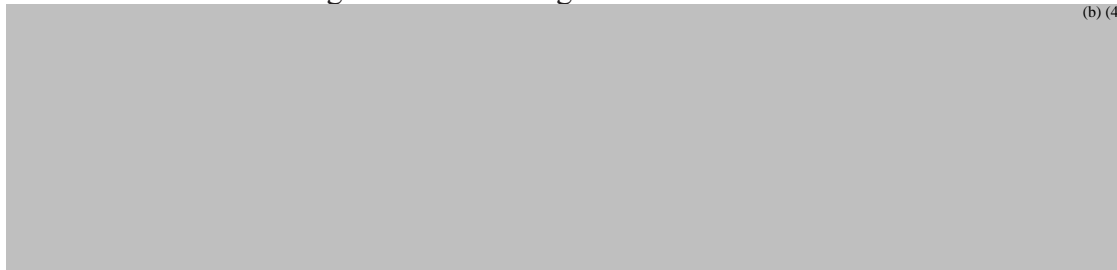
In order to address this usability concern, Armstrong submitted additional device testing data during the second cycle that was used to inform labeling changes. These device testing results are also informative in interpreting the clinical importance of the results of consumer testing. Consumer errors in following labeled instructions that result in meaningful changes to the delivered dose are more critical than those that do not. The following relevant performance parameters were determined:

- Drop testing from a 5 foot height with the inhaler assembled resulted in all units passing acceptance testing.
- Drop testing of the inhaler and canister separately (as would occur during cleaning) resulted in a 1.6% failure rate of the device due to breakage of the valve stem and a 0.17% breakage of the dose counter. There was a minor incidence of overcounting of the remaining units and no undercounting.

- Almost all of the devices (99.2%) delivered only a partial dose after dropping, consistent with the need to prime the device.
- Dose content uniformity demonstrated clogging of actuator orifice beyond 2 days of use (8 actuations per day x 2 days) if the device is not cleaned. Testing of a variety of different cleaning methods demonstrated that a minimum of a 2 second wash prevented clogging. The temperature of the water used, air drying versus quick drying (drying with a paper towel), and washing from both ends did not impact results.
- Failure to shake the device before the initial priming of the device results in a high probability that the first two doses will be superpotent, up to (b) (4) % of the labeled claim due to settling of the suspension.
- Quick dispensing of the priming sprays over 2-3 seconds may result in a subpotent dose.
- Failure to prime throughout the life of the device could result in inconsistent dosing (both over and under dosing), but not overt failure of the device. Priming (shake and spray) prior to subsequent dosing would resolve the dose content uniformity issue.
- Off center actuation may result in a superpotent dose, but not device failure. A concentric ridge around the dose indicator was included to mitigate the risk of a user's finger slipping during actuation.

Of these various failure modes, the ones of most concern are those that result in failure to deliver an adequate dose, or worse yet, no dose at all if the actuator is clogged. While delivery of a superpotent dose is less than ideal and could potentially result in an increased incidence of adverse effects such as tremor or jitteriness, safety data suggest that doubling the dose is unlikely to result in significant immediate harm. In contrast, failure to deliver a dose of a rescue inhaler to a person suffering from an acute asthma attack could result in serious outcomes if the consumer is unable to seek immediate medical assistance.

Based on the device testing data, Armstrong modified labeling to put in more conservative directions for use with the goal of minimizing device failure as follows:



Of note, product labels for other short-acting beta-agonist MDI products on the market in the prescription setting [albuterol (Proventil, Ventolin, and ProAir) and levalbuterol (Xopenex)] recommend weekly cleaning, and priming is not required prior to each use.

The CMC team concluded that Armstrong has adequately investigated potential failure modes for their drug-device product from a manufacturing standpoint. I concur with this conclusion.

4 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

As epinephrine has a long history of use and has been previously approved as a CFC-inhalational product, no additional toxicology data are required to support the active ingredient epinephrine for inhalational use. No toxicology information was submitted in the original NDA application. Letters of authorization were provided to the DMFs for epinephrine and the HFA-124a propellant and deemed acceptable by the pharmacology/toxicology review team. Although the excipient thymol is generally recognized as safe (GRAS) for oral use, there was a lack of data to support chronic use of thymol for inhalational use. The CR letter stated the information needed to address this deficiency was *“Provide information supporting the safety of chronic inhalation of thymol. If such information is not currently available, conduct a repeated dose inhalation toxicity study of 6 months duration in an appropriate species that shows no adverse findings to support the use of thymol in your product.”*

The current submission includes a summary report of two overlapping 6 month repeat dose inhalation toxicity studies in CD-1 mice and a toxicokinetic report from a separate inhalational exposure study. The 6 month studies were merged by the sponsor while the investigations were ongoing. Dr. Thompson, the FDA toxicology reviewer, noted a number of deficiencies in study design and irregularities regarding the in-life observations, and requested a for cause inspection of this study. The inspection of the study site demonstrated a number of deficiencies in documentation and recording of study data; it was determined that the study was not conducted under Good Laboratory Practices (GLP) conditions. After numerous information requests to the sponsor and further discussions between the toxicology review team and the inspection team, the teams concluded that: 1) animals received adequate dosing and exposure to thymol during the study, 2) while the in life observations were not appropriately recorded, tissue collection and histopathological findings were adequately documented, and 3) histopathology results did not show concerning findings. The toxicology team concluded that despite the significant issues with study conduct, the histopathology results in conjunction with the available clinical safety data are adequate to support use of thymol in this product without conducting further nonclinical studies, which resolves the first cycle toxicology deficiency. I concur with this recommendation.

5 SAFETY

The pharmacologic and physiologic effects of epinephrine are well characterized, including stimulation of the sympathetic nervous system to increase heart rate and the force of heart contractions, increase blood pressure, and increase the breakdown of glycogen into glucose resulting in increased blood glucose levels. The β_2 effects of epinephrine include relaxation of bronchial smooth muscles resulting in an increase in bronchial airflow, dilation of blood vessels in skeletal muscles and the liver, release of glucose into the circulation, and inhibition of release of mediators from stimulated eosinophils, mast cells, and basophils. Safety data for epinephrine-HFA was reviewed in light of these known effects of the active moiety.

5.1 Safety in clinical trials

Safety in clinical trials and cardiac safety was reviewed during the first cycle and deemed to be acceptable for approval. The safety profile in the adult Phase 3 trials does not suggest a serious safety signal, although the clinical trial database is small, with 373 adult and adolescent subjects and patients exposed to any dose of epinephrine-HFA. Of these, 248 received more than one dose of drug. In addition, 35 pediatric patients aged 4-11 received more than one dose of epinephrine-HFA.

The most commonly reported adverse event was tremor, which was the one event with a notable imbalance, occurring in 10% of patients in the epinephrine-HFA group compared to 2% in the placebo and epinephrine-CFC groups. This finding is consistent with the non-selective beta-agonist effect of the drug. Other events occurring more frequently in the epinephrine-HFA group compared to control groups were throat irritation, cough, feeling jittery, bronchitis, dizziness, respiratory tract irritation, glossodynia, ligament sprain, and muscle strain.

The high dose PK study in healthy volunteers demonstrated substantial increases in blood pressure (>50 mmHg systolic) and pulse (>60 bpm) in some patients 10 minutes after a single dose of 1250 mcg and 1600 mcg, although the median increases were more modest (pulse increase of 5-6 beats, systolic blood pressure increase of 9-14 mmHg, diastolic blood pressure increase of 1-3 mmHg). To achieve a dose of 1250 mcg, a patient would have to take 10 inhalations of the proposed 125 mcg dose in rapid succession; a dose of 1600 mcg would require 12-13 inhalations. No such changes were observed at the proposed maximal dose of 250 mcg, giving some idea of the safety margin available in the case of overdose. This information is particularly relevant for the application, since failure to shake the device would result in a superpotent dose per spray, up to approximately twice the labeled dose (i.e. a maximal dose of 250 mcg per spray).

5.2 Consumer studies

First cycle

In the first cycle, Armstrong conducted 4 consumer studies, including 3 label comprehension studies and one behavioral (human factors study) evaluating whether subjects could correctly use the device. Given the long history of use of epinephrine CFC, the development program for epinephrine HFA was designed to focus only on elements that differed from the CFC product label, and did not focus on self-selection or safety questions related to the label that are commonly evaluated as part of a de novo OTC program.

The label comprehension studies were iterative and focused on 3 primary communication objectives, all related to the dose indicator. In addition, the label comprehension studies identified limitations in consumers' understanding of the following critical information: the need to prime the inhaler before using the first time, the need to clean the product daily after use, and the need to reprime when wet.

The first cycle human factors study had a number of methodological issues. However, suboptimal performance in several key areas that could impact device performance were noted, with only 74% of subjects shaking the MDI prior to priming, 82% priming prior to use, 64% correctly washing the mouthpiece through the top opening, and 74% shaking the

MDI prior to use. Some consumers had difficulty removing the canister to clean the product, and the study did not assess whether consumers correctly reassembled the product after cleaning. Incorrectly completing these steps could cause dose variability and clogging with resulting failure to deliver the appropriate dose, a potential issue for both safety and efficacy.

Second cycle label comprehension studies

In the second cycle, Armstrong conducted three additional label comprehension studies followed by a human factors study. Label comprehension studies were iterative and focused on optimizing understanding of cleaning, priming, placing finger in the center of the dose indicator to spray, and not to rely on the dose indicator if the product is dropped. Overall, these results demonstrated that consumers continued to demonstrate less than optimal comprehension for priming objectives, particularly in the low literacy population (lower bound of the confidence interval 66-77% answering correctly depending on the question). Former Primatene CFC users generally scored more poorly than non-Primatene users. Based on these results, Armstrong substantively simplified instructions for use and added additional diagrams. For example, the priming instructions were modified from

(b) (4)

Rather than retesting the newly modified label in further label comprehension studies, the sponsor moved on to a human factors study with the revised label. This approach is reasonable given that the major elements being tested were related to instructions for use.

Based on feedback from the Advisory Committee, Armstrong also assessed label comprehension of three safety warnings: 1) "Children under age 12, do not use", 2) "Do not use more than 8 inhalations in 24 hours," and 3) "See your doctor if you have more than two asthma attacks in one week." Results showed good comprehension in both normal and low literacy populations of "Children under age 12, do not use" and "See your doctor if you have more than two asthma attacks in one week", with 97% and 98% of the overall population answering correctly. "Do not use more than 8 inhalations in 24 hours" scored less well, with 92% [95% CI (89%, 94%)] of the overall population and 89% [95% CI (82%, 94%)] of the low literacy population answering correctly. Of note, this warning is worded more conservatively than the monograph warning, which permits up to 9 doses in a 24 hour period, so was deemed acceptable by the social science and clinical teams.

Second cycle human factors study

Because the drug facts label (DFL) and consumer instructions for use (CIL) were changed substantially subsequent to the final label comprehension study, the human factors study is much more relevant to the overall expected use of the product by consumers, and thus is a key basis for regulatory decision making. The second cycle human factors study was conducted at two different U.S. testing facilities in 151 adult and adolescent subjects aged 12 to 17 years. Overall the population included 133 adults and 18 adolescents, of whom 22 (19 adults and 3 adolescents) were low literacy. Thirty-two adult and 7 adolescent subjects had previously used inhalers. Subjects performed 3 simulated-use tasks, and then responded to open-ended questions to assess three label comprehension elements related to understanding the dose indicator. The three primary endpoints evaluated the simulated use tasks of 1) initial priming of the inhaler to prepare it for use, 2) cleaning the inhaler, and 3)

routine use of the inhaler. For the primary endpoints in the sponsor's analyses, subjects were scored as *Completed*, *Completed with Issues*, or *Not Completed*. *Completed with Issues* was defined as subjects who struggled initially to perform the task but self-corrected during the study or performed the task in a way that deviated from the instructions. Subjects were also scored as *Completed with Issues* if they completed the task successfully after being referred to the instructions by the study moderator. In these cases, the moderator would ask the participant if he/she had performed the task in a way that differed from the instructions. Secondary label comprehension endpoints evaluated how to interpret the dose indicator, not relying on the dose indicator if dropped, and understanding correct finger positioning to ensure the device delivers medication properly with each spray. The study tested performance in a single setting, and did not retest at a subsequent time point to determine whether subjects were able to continue using the product correctly as a simulation of intermittent use.

The first primary endpoint, initial priming of the inhaler to prepare it for use required the subject to shake the inhaler then spray it into the air, repeating the shake/spray sequence four times prior to first use. The second primary endpoint, cleaning, required the subject to demonstrate removal of the canister from the actuator and running water through the actuator to clean the spray orifice for at least 15 seconds (the label states 30 seconds). The third primary endpoint, routine use, required the subject to shake and spray into the air (single prime) prior to dosing, then close the lips around inhaler and press down squarely on the top of the actuator while inhaling. Results are shown in Table 2.

Table 2: Human Factors Study Completion and Failure Rates

	Failed to Complete Primary Objective (N=151)		
	Not Completed	Not Completed OR Completed with Issues	Not Completed OR Completed with Clinically Important Issues
Task 1: First Use	8 (5%)	46 (30%)	20 (13%)
Task 2: Cleaning	4 (3%)	60 (40%)	18 (12%)
Task 3: Routine Use	2 (1%)	23 (15%)	19 (13%)
Failed any task	12 (8%)	92 (61%)	45 (30%)

Data adapted from Armstrong Human factors engineering report, AMP-2016-E004-G3-601 and review by the Division of Medication Error Prevention and Analysis

The sponsor considered a "failure" to be only those subjects who did not complete a task (in Table 2 see column designated as Not Completed, 8% failed any task). However, review by the Division of Medication Error Prevention and Analysis recommended more conservative assessment noting that because the product is intended for OTC use, consumers would not have a study moderator to direct them to review the instructions in case of failure to complete the task. In the most conservative approach, only 39% of subjects were able to complete all 3 tasks successfully without correction (in Table 2 see

column designated as Not Completed OR Completed with Issues, 61% failed any task). Of those subjects who completed a task with issues, some were able to self-correct, and others deviated from the instructions for use in ways that would have resulted in correct dosing despite the use error. However, many subjects who completed the task with issues actually failed the task in a clinically important way that could have resulted in overdosing, underdosing, or failure to deliver a dose (e.g. clogging) and required a study moderator to redirect them. In order to determine how many subjects failed in clinically important ways, DMEPA reviewers, with input from the clinical, statistics, and chemistry review teams, adjudicated each subject to determine if the particular error would have potentially resulted in a clinically important device issue. For example, there were 15 subjects who failed to remove the canister from the actuator prior to washing, which does not clean the spray orifice and would likely result in clogging with subsequent failure to deliver a dose. Since failure of any one of the three tasks may have clinically important implications, the statistical team analyzed the data to determine how many subjects failed any single task of the three. Overall, this analysis determined that 30% of subjects failed one or more of the three critical tasks in a clinically important way (in Table 2 see column designated as Not Completed OR Completed with Clinically Important Issues, 30% failed any task).

The sponsor justifies failure of task 1 by postulating that subjects who failed the priming sequence prior to first use would have gotten an appropriate dose eventually if they performed the routine use task correctly. This is theoretically true; however, doses delivered before adequate priming would have most likely resulted in overdosing of up to two times the labeled dose. Since safety data from the PK study support this dose for short-term use, this outcome is of less concern than failures of task 2 or 3, which may result in failure to deliver a dose or in underdosing. Based on the adjudicated analysis, there were 11 subjects who failed only task 1 (first use) and had adequate performance on tasks 2 (cleaning) and 3 (routine use). Even if these subjects were not considered to be failures, this still gives a total failure rate of 34/151 (23%), which remains concerning for a rescue inhaler.

The secondary label comprehension objectives for the dose indicator and finger positioning tested well. Only a small number of subjects failed to understand the dose indicator (2/151) or the potential for malfunction if dropped (4/151). Encouragingly, all 151 participants understood correct finger positioning and how to hold the inhaler correctly. This was initially raised as a potential concern because failure to hold the inhaler upright could result in discharge of propellant only and eventual failure to deliver a dose.

In considering the implications of the failures observed during human factors testing, it is important to understand that the human factors study represents a best case scenario because subjects were observed under conditions of low stress and were supplied with both the packaging (including the DFL) and the CIL. Consumers actually using the inhaler may or may not have the instructions for use immediately available. Further, since the product is used as a rescue inhaler for intermittent asthma, consumers will likely be experiencing dyspnea and some degree of respiratory distress at the time of use, which may preclude substantial time to read and comprehend labeling.

The Division of Medication Errors and Prevention review team concluded that the human factors study was unable to demonstrate that the intended user population is able to use the

product safely and effectively. Because approximately 30% of use errors observed in the study could result in clinically important dosing issues, I concur with this assessment. They also note that use errors are observed in post-marketing experience with prescription HFA inhalers. Given the nature of these types of inhalers, there is likely to be some degree of use errors no matter how the use instructions are optimized. However, if inhaler issues arise or lack of efficacy occurs in the prescription setting, consumers are able to call the prescribing physician, which is not available for an OTC product. Therefore, minimizing use errors to the lowest possible level is essential for safe and effective OTC use.

Differences between epinephrine-HFA and Primatene Mist[®]

Apart from the obvious differences in propellant and inhaler design, a number of differences exist between the epinephrine-HFA and the previously-marketed epinephrine-CFC product. It is likely that consumers who previously used and are familiar with the CFC product will also use the epinephrine-HFA product. As such, it is possible that confusion may occur for patients purchasing the product in the OTC setting without assistance of a healthcare intermediary. These differences were described in my first cycle review; however, I reiterate them here because it is important to understand that compared to CFC versions HFA inhalers require much more diligent adherence to labeled instructions in order to obtain the correct dose. Consumers may also be familiar with various dry powder inhalers (DPIs) on the market, which have very different labeled instructions for use.

- The formulation for epinephrine-HFA is a suspension rather than a solution as for the CFC product. As such, the MDI must be shaken prior to use to prevent settling. If the MDI is not shaken, this could potentially result in dose variability leading to higher doses administered.
- Epinephrine-HFA must be cleaned daily to prevent clogging. In contrast, because CFC propellants also function as cleaning agents, daily cleaning was not required for epinephrine-CFC.
- Epinephrine-HFA must be primed prior to each use. Priming was not required for epinephrine-CFC.
- Epinephrine-HFA contains a dose counter whereas the epinephrine-CFC product had a transparent glass reservoir allowing patients to visually determine when the drug solution was running out.
- The proposed population for epinephrine-HFA is adults and adolescents age 12 and older, while the CFC product was approved down to age 4.
- Pharmacokinetic studies demonstrate that there are greater systemic blood levels with epinephrine-HFA compared to epinephrine-CFC. In particular, the C_{\max} is 4.5 times higher.
- The dosing instructions for epinephrine-HFA are different from the CFC product. The proposed dosing for epinephrine-HFA is one to two inhalations per dose not more often than every 4 hours, and not to exceed 8 inhalations in 24 hours. Dosing for epinephrine-CFC was one or two inhalations every 3 hours with no maximum.

- The sponsor notes the following advantages of epinephrine-HFA compared to the CFC product: 1) elimination of the CFC propellant to meet the requirements of the Montreal Protocol, 2) proposed dose is reduced by 43% with similar efficacy, 3) the pH of the new formulation is neutral rather than acidic, 4) amount of alcohol in the formulation (b) (4) which can reduce false positive Breathalyzer tests, and 5) an aluminum canister replaces the glass bottle.

Actual use study

The clinical deficiency defined in the CR letter cited concerns about consumers' ability to use the epinephrine HFA product. To resolve this deficiency, the letter stated that data are required to support consumer's ability to use epinephrine HFA in the OTC setting. Steps were listed as follows: 1) revise the labeling to optimize comprehension and assess the revised label in a label comprehension study, 2) conduct a human factors study to assess consumers' ability to use the product, and 3) conduct a randomized actual use study to rigorously quantify and evaluate complaints or problems associated with use of the product. The sponsor chose not to conduct an actual use study, citing that because consumers would use this product only intermittently, it would be difficult to obtain sufficient use to show complaints. Although epinephrine HFA is indicated for only intermittent use, I disagree with this conclusion. Data from a nationwide household survey to determine the demographic patterns and use profiles of the former Primatene Mist CFC inhaler users demonstrated that 36% used the product < 1 time per month, 35% used 1 to 4 times per month, and 29% used > 4 times per month.² Given the failure mode analysis this amount of use over a several month timeframe should be sufficient to determine how many subjects report "device malfunction". Subjects with device issues could then be evaluated at a study site to determine how they were using their inhaler. Such testing could potentially be useful, particularly if extremely novel types of labeling elements are introduced in order to improve use failures. However, I do agree that it would take an impractically large study if the endpoint were related to asthma outcomes, which is the ultimate concern. I also agree that human factors testing is more useful in evaluating exactly how consumers may interact with the device, which could be extended to more than one session to simulate intermittent use.

5.3 Safety conclusions

The sponsor has taken a number of steps during this review cycle to improve and simplify labeling and instructions for use. Armstrong also conducted robust device testing to identify the clinical implications of various use errors, using this data to take a conservative approach to labeling. Given that device failures related to use errors are also reported with prescription HFA inhalers, it seems unlikely that any labeling changes will be able to result in perfect adherence to labeled instructions. However, I remain concerned that 30% of users in the human factors study had use errors that could result in clinically important dosing errors, 23% of which would likely result in underdosing or failure to deliver a dose at all, and believe this error rate can be improved. The usability issue is especially problematic for an OTC product because consumers will be using the device without the oversight of a

² Dickenson, BA, et al. Safety of Over-the-Counter Inhalers for Asthma: Report of the Counsel on Scientific Affairs, American Medical Association, Chest 2000; 118:522-26.

health care professional who the user might call if there is a problem. Ability to correctly use the device is even more concerning considering that this product is indicated for acute relief of asthma symptoms, which if not treated promptly may result in adverse asthma outcomes.

6 ADVISORY COMMITTEE MEETING

During the first review cycle, the application was discussed during a joint meeting of the Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee. The majority of the committee did not agree that the risk/benefit profile of epinephrine inhalation aerosol 125 mcg per actuation supported OTC use for the temporary relief of mild symptoms of intermittent asthma. The vote was 6 yes, 18 no, and 1 member did not vote. Committee members voted “No” primarily due to safety concerns, including: a lack of long-term safety data, limited data on use by adolescents 12-18 years of age, the device and dose indicator have issues that could impact safe use, consumers’ inability to adequately assess the severity of their asthma, the need for a learned intermediary to adequately educate asthma patients about their diagnosis, and national guidelines recommending against use of epinephrine for the treatment of asthma. Since there were no new issues, the application was not discussed in an advisory committee meeting during this review cycle.

7 PEDIATRICS

Pediatric patients aged 12 and above were included in the adult asthma trials performed to support efficacy and safety of this application. A 4 week efficacy trial in pediatric patients aged 4-11 years was conducted, but was underpowered and failed to demonstrate statistically significant efficacy. As such, Armstrong is not currently seeking an indication in children aged 4-11 years. Another efficacy trial in children aged 4-11 years is ongoing, and the Pediatric Review Committee (PeRC) agreed to a waiver under age 4 years. The previously marketed epinephrine CFC formulation was approved down to age 4. Details regarding pharmacokinetic data in children required under PREA are ongoing at the time of this review, and will be resolved in subsequent cycle(s).

8 LABELING

8.1 *Proprietary name*

The sponsor proposed the proprietary names (b) (4) (December 12, 2013) and (b) (4) (April 16, 2014). Members of the Advisory Committee raised the concern that a name, that uses the same root name Primatene as the CFC formulation, known as Primatene Mist, could lead to consumer confusion and increase user error with the device due to the large number of differences between the products. This concern was echoed by the social science and clinical OTC teams during the first review cycle. During the second cycle review, (b) (4)

The name Primatene Mist was once again

submitted. Due to the length of time that the CFC inhaler has been off the market, the issue with confusion was considered to be less relevant, so the name Primatene Mist was found acceptable.

8.2 Consumer labeling

Given the Complete Response Action, a full labeling review was not conducted during the first review cycle. During this second cycle, a complete labeling review was performed by the interdisciplinary science team, with input from DMEPA, the clinical team, the CMC team, and the social science team. A number of recommendations were conveyed to the sponsor, primarily related to Drug Facts specifications and consistency of language throughout the principal display panel on the outer carton, the DFL on the outer carton, the abbreviated DFL on the metal canister, and the CIL. Armstrong agreed to these changes. The DFL and CIL include a reference to a website, which contains information about asthma in general, the epinephrine HFA product, and several videos on how to use the product. The labeling team also reviewed the website and has several suggestions about content and consistency.

The major question for this application is whether the product can be adequately labeled such that consumers can use the product correctly without the intervention of a health care professional. The team carefully considered whether the labeling has been completely optimized to allow for correct use or if other elements could be considered. It is clear from the human factors study performed with the current iteration of the product label that understanding how to use the device remains problematic. While the labeling team has additional suggestions for the DFL and CIL that will be communicated to the sponsor in the CR letter, it is unclear whether these changes would be sufficient to significantly impact usability. Two areas that have not been explored are labeling of the inhaler itself and the website.

Currently, the orange-colored actuator has embossed printing on the front panel with instructions regarding shaking before use and cleaning; however, these instructions are not completely consistent with the rest of labeling. In addition, (b) (4)

The abbreviated DFL that is present on the metal canister is not visible without removing the canister from the actuator and the print is very tiny. Because the user may not have immediate access to the DFL or CIL when the inhaler is being used, emphasizing proper use instructions on the actuator may have significant benefit in reminding consumers of key use steps. Pictograms may also be helpful. No prescription inhaler has a similar presentation, so re-testing this change in a human factors study is necessary. It is important that any labeling on the actuator does not change the composition of the actuator or the flow pattern of the drug, since this could introduce variations in spray characteristics potentially impacting efficacy.

Although referenced in the product labeling, the sponsor intended the website to be an adjunct to labeling rather than a required element, and the website has not been tested in consumer studies. Considering a website as a required element in product labeling would be precedent setting in the OTC setting, and I do not recommend doing so at this point. However, if adequate understanding of use cannot be demonstrated with more traditional

approaches to labeling, this element or other creative visual approaches to aid usability could be considered.

9 DECISION/ACTION/BENEFIT RISK ASSESSMENT

9.1 *Regulatory action*

Armstrong has not submitted adequate data to support approval of epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA), at a dose of 125 mcg/actuation for over the counter (OTC) use for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. Two of the three deficiencies raised in the first cycle review were resolved. However, the clinical deficiency from the first cycle, namely that the sponsor has not adequately demonstrated that consumers can use the drug-device product safely and effectively without the intervention of a health care professional is not adequately resolved. Specifically, data from the human factors study conducted after several rounds of label optimization shows that at least 30% of subjects had clinically important use errors that could result in overdosing, underdosing, or failure to deliver a dose altogether.

To resolve this deficiency, Armstrong will need to further optimize labeling including making the instructions for use present on the actuator both visible and consistent with the CIL. Subsequently, Armstrong will need to conduct a human factors study demonstrate that consumers can appropriately use the device with the optimized labeling. Since novel changes to labeling can sometimes paradoxically make adherence worse, testing is especially critical. Although the sponsor chose to conduct an extremely large human factors study during this cycle, a smaller number of subjects consistent with FDA guidance on human factors testing would likely be sufficient. Depending on the elements introduced into labeling and the results of human factors testing, an actual use study may or may not be helpful.

9.2 *Risk Benefit assessment*

Potential benefits of this product if approved and used correctly include that epinephrine HFA relate to the increased access OTC availability provides to consumers. For consumers with mild, intermittent asthma, being able to purchase a rescue inhaler in the OTC setting could supplement prescription medication for cases in which a prescription had run out or was unavailable. However, if the inhaler doesn't work (e.g. through clogging or subtherapeutic dosing), having it available could do more harm than good by providing the consumer with a false sense of security that leads to not seeking medical help early in the course of an exacerbation.

Taking these factors into account, the overall risk-benefit assessment does not support OTC approval of epinephrine HFA for the temporary relief of mild symptoms of intermittent asthma. The major issue of concern is consumers' ability to use the product correctly in the OTC setting. Because this product is indicated for acute relief of asthma symptoms, which if not treated promptly may result in serious adverse asthma outcomes, taking every possible step to ensure that consumers are able to use the inhaler safely and effectively is critical. While it will likely not be possible to completely eliminate use errors, it is

necessary to minimize those that result in clinically important dosing errors as much as possible. The human factors study demonstrating that 30% of subjects have clinically important use errors does not give sufficient confidence that this product can be successfully used if approved, especially since the human factors study represents a best case situation.

9.2.1 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

9.4 Recommendation for other Postmarketing Requirements and Commitments

None due to Complete Response action.

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/s/

THERESA M MICHELE
12/23/2016

Summary Review for Regulatory Action

Date	May 21, 2014
From	Theresa M. Michele, MD Director, Division of Nonprescription Clinical Evaluation
Subject	Division Director Summary Review
NDA/BLA #	205,920
Applicant Name	Armstrong Pharmaceuticals, Inc.
Date of Submission	July 22, 2013
PDUFA Goal Date	May 22, 2014
Proprietary Name / Established (USAN) Name	Epinephrine Inhalation Aerosol
Dosage Forms / Route of Administration / Strength	Aerosol, metered / Inhalation / 125 mcg/actuation
Proposed Indication(s)	Temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older
Regulatory Action	Complete Response

1 INTRODUCTION

Armstrong Pharmaceuticals, Inc. (Armstrong) submitted this 505(b)(2) new drug application seeking approval for epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA), at a dose of 125 mcg/actuation for over the counter (OTC) use for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older.

Epinephrine-HFA is a short-acting beta₂-agonist (SABA) bronchodilator used as a quick relief medication for acute bronchospasm. Armstrong is positioning the epinephrine-HFA MDI (metered dose inhaler) as an alternative to the previously marketed Primatene[®] Mist epinephrine MDI, which was removed from the market in 2011 due to the phase out of ozone-depleting chlorofluorocarbon (CFC) propellants under the Montreal Protocol. Of note, this product was not removed from the market due to reasons of safety or efficacy.

Armstrong's development program for epinephrine-HFA consisted of three single dose pharmacokinetic (PK) trials in healthy volunteers, two single dose, dose-ranging trials in adults with asthma, a 12 week Phase 3 safety and efficacy trial in adults and adolescents with an additional 12 week safety extension, and a 4 week safety and efficacy trial in children aged 4 to 11 years. The Phase 3 trials were placebo controlled, and the adult trial also included an epinephrine-CFC comparator arm. In addition, the sponsor conducted 4

consumer studies, including 3 label comprehension studies and one behavioral (human factors study) evaluating whether subjects could correctly use the device.

As this product would represent the only MDI product available for OTC use, this application was presented to a joint meeting of the Nonprescription Drugs Advisory Committee (NDAC) and Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting on February 25, 2014. At this meeting, FDA presented concerns regarding the device performance given the relatively high number of device malfunctions and dose indicator errors reported in the clinical program. In response to these concerns, Armstrong submitted additional analyses of device and dose indicator performance on February 24, 2014, updated analyses on March 18, 2014, and responses to information requests on April 2 and May 12, 2014. These additional analyses have all been reviewed in detail during this review cycle.

This summary review will provide an overview of the application, with a focus on the clinical and consumer studies and the device issues. Due to personnel changes within the Division, this review serves as both a Division Director review and CDTL review.

2 BACKGROUND

2.1 Asthma

Asthma is a chronic inflammatory disease of the airways characterized by varying and recurring symptoms of shortness of breath, chest tightness, wheezing and cough, airflow obstruction, bronchial hyper-responsiveness, and underlying inflammation. In the United States, asthma affects more than 22 million persons. It is one of the most common chronic diseases of childhood, affecting more than 6 million children. Worldwide, about 300 million people are affected.^{1,2}

Asthma is classified into four categories based on the level of symptoms, nighttime awakening from symptoms, SABA bronchodilator use for symptom control, interference with normal activity, and lung function as well as the risk of exacerbations. To establish a diagnosis of asthma, the NHLBI National Asthma Education and Prevention Program (NAEPP) Guidelines¹ state that the clinician should determine that:

- Episodic symptoms of airflow obstruction are present
- Airflow obstruction is at least partially reversible, and
- Alternative diagnoses are excluded

The four categories of asthma are Intermittent, Mild Persistent, Moderate Persistent, and Severe Persistent. Classification of asthma based on severity is useful when deciding about

¹ National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication nu. 08-4051). Full text available online: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

² Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, Updated 2007. Full text available online: www.ginasthma.com

management at the initial assessment of a patient. When a patient is already on treatment, asthma severity classification reflects both the severity of the underlying disease and its responsiveness to treatment. Adults and adolescents aged 12 years and older with intermittent asthma are expected to have symptoms 2 or fewer days per week, nighttime awakenings 2 or fewer times per month, use a short-acting beta agonist for symptom control 2 or fewer days per week, have no interference of normal activities by asthma symptoms, have normal baseline lung function, and experience one or fewer exacerbations per year. Although exacerbations can still be severe, SABA taken as needed to treat symptoms is usually sufficient therapy for intermittent asthma.¹

The proposed Drug Facts label for epinephrine-HFA proposes an indication for “mild symptoms of intermittent asthma” which includes patients with intermittent asthma only. In addition, the label contains a “Do not use unless a doctor said you have asthma.” This indication and warning are consistent with the previously marketed epinephrine-CFC product.

2.2 Available medications

Medications for asthma are categorized into two classes: quick-relief medications used to treat acute symptoms and exacerbations and long-term control medications used to achieve and maintain control of persistent asthma¹. There are several drug classes available for the quick relief of airflow obstruction in patients with asthma. Approved quick relief medications are limited to SABAs, although short-acting anticholinergic agents are also used off-label as an alternative in patients who do not tolerate SABAs. Long-term control medications include inhaled and systemic corticosteroids, cromones, leukotriene receptor antagonists, long-acting beta-agonists (recommended only in combination with inhaled corticosteroids), omalizumab, and methylxanthines.

Inhaled SABAs are the mainstay of therapy for the acute treatment of bronchospasm in both routine outpatient management and in the hospital setting. Prescription SABAs include albuterol and levalbuterol. These have a relatively quick onset of bronchodilation that lasts for about 6 hours. Adverse reactions of inhaled SABAs are typical beta-adrenergic effects, such as increases in heart rate and blood pressure, muscle tremor, and metabolic effects, such as increase in blood glucose and decrease in serum potassium. The inhaled SABAs available by prescription are relatively selective beta₂-agonists.

Epinephrine is a non-selective alpha and beta agonist. Concerns were raised about the possible link between the use of inhaled epinephrine and a slight rise in asthma-related death in the 1940s.³ The 1950s and 1960s brought the introduction of new inhalation products for asthma to the market worldwide, including non-selective (β₁ and β₂) SABA such as isoproterenol and fenoterol, which were both implicated in an increase in asthma-related deaths in certain countries outside of the United States.^{3,4,5,6,7} The use of these

³ Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. *J Allergy*. 1948;19:129-140.

⁴ Van Metre TE. Adverse effects of inhalation of excessive amounts of nebulized isoproterenol in status asthmaticus. *J Allergy*. 1969;43:101-113.

⁵ Crane J, Pearce N, Flatt A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-83: case-control study. *Lancet*. 1989;1:917-922.

⁶ Grainger J, Woodman K, Pearce N, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-1987: a further case-control study. *Thorax*. 1991;46:105-111.

relatively non-selective beta agonists was eventually replaced by more selective (β_2) short-acting beta agonists, e.g., albuterol and levalbuterol. Albuterol, which may be delivered by MDI or electronic nebulizer, is used broadly today as the quick-relief medication of choice for asthma.

The 2007 NAEPP Expert Panel Report 3 recommends short-acting beta₂-agonists as the drug class of choice for rescue treatment, describing SABAs as “the most effective medication for relieving acute bronchospasm.”¹ The 2007 NAEPP also notes that currently available SABAs “have few negative cardiovascular effects.” This stands in contrast to the NAEPP assessment of epinephrine and other less selective adrenergic agents:

The less beta₂-selective agents (isoproterenol, metaproterenol, isoertharine, and epinephrine) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.

In contrast to the asthma-specific indication previously approved for epinephrine-CFC MDIs and proposed for epinephrine-HFA, the indication for prescription SABAs are for general bronchodilation (“treatment or prevention of bronchospasm with reversible obstructive airway disease”) rather than for a specific disease, such as asthma or chronic obstructive pulmonary disease (COPD). Given that the indication for other SABAs is for general bronchodilation, it seems likely that some consumers may use epinephrine-HFA off-label for other indications, such as COPD.

2.3 Relevant Regulatory History for Epinephrine

Epinephrine, one of the first sympathomimetic agents in medicine, has been marketed in the United States in a variety of different formulations since 1901, with use in the treatment of asthma dating back to the early 1900s. The first route of administration widely used was intravenous or subcutaneous injection; later, administration by oral inhalation was adopted. Epinephrine in an MDI formulation utilizing CFCs (Primatene[®] Mist) was approved for OTC use for the treatment of symptoms of asthma in 1967 under NDA 16-126 (Wyeth). A generic version was approved under ANDA 87-997 (Armstrong) in 1984. Armstrong subsequently purchased the Primatene Mist trademark for their product, and Wyeth discontinued their product.

CFCs are organic compounds that are broken down by strong ultraviolet light in the stratosphere. CFC breakdown releases chlorine atoms that deplete the ozone layer, resulting in increased levels of ultraviolet-B radiation that may increase cataracts and skin cancer. Beginning in 1996, MDIs using CFC propellants began to be phased out to protect the environment under the Montreal Protocol on Substances that Deplete the Ozone Layer. The process for the phase out of CFC use for epinephrine MDIs began in 2006 with an FDA advisory committee meeting, a proposed rule in 2007, and a public meeting in 2007. In the 2007 proposed rule, FDA proposed an end date (effective date) of December 31, 2010, for the use of CFCs for epinephrine MDIs. In comments on the proposed rule, the manufacturer of epinephrine CFC MDIs requested additional time (December 31, 2011) to reformulate the product. The Final Rule was published in 2008 and based upon a request

⁷ Westendrop RG, Blauw GJ. End of New Zealand asthma epidemic. *Lancet*. 1995;345:985.

from the manufacturer, the end date (effective date) for use of CFCs for epinephrine MDIs was December 31, 2011⁸.

Armstrong began interacting with FDA regarding reformulation of epinephrine without CFCs in a pre-IND meeting in 2007 (IND 74,286), after publication of the proposed rule. The Agency provided extensive feedback to the sponsor throughout the development program, including multiple communications outside of traditional milestone meetings. Meetings included joint input from the Division of Pulmonary Allergy and Rheumatology Products and the Division of Nonprescription Clinical Evaluation. Key interactions are summarized below.

- **March 27, 2007 pre-IND meeting**
 - Discussion of proposed epinephrine HFA-MDI development program, including requirements for clinical efficacy and safety, consumer behavior studies, and data to support the reliability and robustness of the device and dose counter.
- **November 25, 2008 Communication**
 - Feedback provided on clinical trial design
- **October 26, 2009 IND submitted**
 - Feedback provided on proposed development program, including the need for detailed monitoring of cardiovascular vital signs, pharmacokinetic sampling, long-term safety data, consumer studies, and data to support the chemistry, manufacturing, and controls of the product.
- **October 29, 2010 EOP2 Meeting**
 - Dose-ranging did not appear to be adequate; exposure of 125 mcg dose higher than reference product; recommendation to explore doses lower than 125 mcg
 - Recommendation for larger and longer pediatric clinical trial
 - Include reference product in Phase 3 trials
 - Assess device performance, including ruggedness and reliability
- **May 10, 2011 Communication**
 - Based on preliminary results of the dose ranging trials, FDA recommended carrying forward the epinephrine HFA 125 mcg dose into the Phase 3 program, noting that the systemic exposure from 125 mcg is higher than that with Primatene 220 mcg, a difference that will have to be supported by Phase 3 data and addressed in the NDA
- **September 23, 2011 preNDA meeting**
 - Reiteration of the need for a minimum of 6 months of safety data
 - A large (n~300) label comprehension/behavioral use trial is required
 - Concerns raised regarding the product's potential need for once-daily cleaning. FDA requested device performance data under different in-use conditions to assess the impact of not cleaning the mouthpiece as directed.
 - Reminder to assess potential malfunctioning of the device with real-life usage

⁸ Federal Register Volume 73, no 224: 21 CFR Part 2: Use of Ozone-Depleting Substances; Removal of Essential-Use Designation (Epinephrine) Final Rule; Nov 19, 2008.

- Recommendation that the Sponsor request a second pre-NDA meeting upon the completion of phase 3
- **January 26, 2012 Communication**
 - Feedback provided on proposed long-term safety trial
 - Requested safety data from at least 300 patients exposed for 6 months, which could be generated from already ongoing trials or from a new separate long term safety trial
 - Requested pharmacodynamic data (i.e., blood pressure, heart rate)
 - Deferred discussions of the pediatric program until efficacy and safety data in adults and adolescents were available
- **April 23, 2012 Communication**
 - Feedback provided on proposed label comprehension study
- **January 31, 2013 2nd preNDA meeting**
 - Recommendations on submission of specific pharmacodynamic data, AEs, serial FEV1 data and literature review in NDA submission
 - Recommendation that NDA submission include evaluations of device performance during real-life use, evidence of device ruggedness, and a discussion of the potential for device clogging as well as justification for device cleaning instructions
 - Concerns raised regarding adequacy of data in pediatric patients 4 to 11 years of age. The sponsor stated they may submit the NDA for adults 18 years of age and older. FDA raised concern that the Primatene Mist CFC product was labeled down to 4 years of age and consumers may use an epinephrine HFA product in patients down to 4 years of age. FDA advised the sponsor to submit all pediatric data with the NDA application, even if the age range proposed for approval is limited to adults.
- **April 8, 2013 NDA 205,496 submitted for epinephrine-HFA (refuse to file)**
 - The application had a number of deficiencies that precluded substantive review (refuse to file letter issued July 7, 2013)
- **July 22, 2013 NDA 205,920 resubmitted for epinephrine-HFA and accepted for filing**
 - A new NDA number (NDA 205,920) was provided because of the vast technical problems associated with the original NDA (205,496)

3 CHEMISTRY, MANUFACTURING, AND CONTROLS

3.1 Active ingredient

The active ingredient, epinephrine, is a phenylethylamine in the class of naturally occurring endogenous hormones and neurotransmitters called catecholamines, which include epinephrine, norepinephrine, and dopamine. Epinephrine is produced by the adrenal medulla. It is a non-selective (both alpha and beta) adrenergic receptor agonist that results in the physiologic effects of vasoconstriction, increased peripheral vascular resistance,

increased cardiac contractility and heart rate, decreased mediator release, and bronchodilation.

The (b) (4) drug substance is manufactured at (b) (4) facility in (b) (4). The drug substance is (b) (4). The drug substance produced by (b) (4).

All DMFs associated with this drug substance were found to be acceptable. Manufacturing and testing facilities associated with the drug substance do not have an acceptable GMP recommendation from Office of Compliance, which results in a Complete Response recommendation for this application from the CMC review team and precludes approval.

3.2 Epinephrine HFA MDI

The epinephrine HFA MDI includes a 14 ml anodized aluminum canister with (b) (4) metering valve (Model (b) (4) 50 µl metering (b) (4)), a top mounted dose indicator ((b) (4) Part No. (b) (4)), and an orange L-shaped actuator (b) (4) with a red dust cap. The canister contains a (b) (4) suspension of epinephrine in propellant HFA-134a, ethanol, thymol (b) (4) and polysorbate 80 (b) (4). Thymol is not found in other currently marketed inhalational products. Each epinephrine HFA MDI contains 160 metered dose inhalations releasing 125 mcg of epinephrine per actuation.

The proposed dose is one or two inhalations with instructions to wait at least 4 hours between doses, with a maximum of 8 inhalations per 24 hour period. The product is a standard press-and-breathe MDI that comes assembled. In order to use the device, the instructions on the package insert state that it must first be shaken and primed. It must also be primed if not used for more than 2 days, if it is still wet after cleaning, or if it is dropped. In addition, the inhaler must be shaken immediately prior to dosing. The instructions also require cleaning by disassembling the device and washing with warm water on a daily basis. According to the sponsor, holding the inhaler with the dose indicator up during actuation is important because otherwise it could cause only the propellant to be discharged. If this process were continued over the life of the product, the propellant may be completely discharged and the inhaler would fail to provide any medication.

The epinephrine HFA MDI includes a top mounted dose actuation indicator. This device attaches to the end of the drug product canister using an adhesive label. The dose indicator mechanically counts each actuation. The display advances every 10 actuations and is labeled numerically in increments of 20. When 20 or fewer actuations remain, the display begins to turn red in color. The red zone continues to fill the display until the counter indexes to zero. At this point the display is at the zero count and completely red, indicating the need to replace the inhaler. After the zero count has been reached, additional actuations of the MDI no longer advance the display. The package instructions note that a finger must be placed on the center of the dose indicator during actuation. Instructions also note that if the MDI is dropped, the dose indicator is no longer reliable and patients must keep track of the number of sprays taken.

Given the significant issues with patient reports of device and dose indicator performance identified in the clinical trials (see Section 3.3), two independent CMC reviews of device

and dose indicator were conducted. Reviewers with particular expertise in MDI drug products were included in both reviews. The reviews independently concluded that the device and dose counter function acceptably when used exactly as labeled and that the labeled instructions for use are supported by simulation data. However, failure to follow the instructions for daily cleaning, drying, and priming (before first use, when wet, when dropped, and if not used for more than 2 days) and instructions regarding dropping may result in a variety of different device performance issues including dispensing of a variable dose, device clogging, and dose indicator miscounting.

Of concern from a clinical standpoint is the issue of cleaning, since failure to clean the device properly may result in clogging. Simulation testing demonstrates that epinephrine HFA devices that are not cleaned fail specifications for both dose content uniformity and shot weight beginning on Day 4 of use. Based on this, instructions for use require daily cleaning if used. Of note, product labels for other short-acting beta-agonist MDI products on the market [albuterol (Proventil, Ventolin, and ProAir) and levalbuterol (Xopenex)] recommend weekly cleaning.

Based on CMC requests, the sponsor agreed to more stringent specifications for dose content uniformity that are consistent with other SABA products. In addition, the CMC team recommends that the sponsor incorporate acceptance criteria for accuracy into the dose indicator specification.

3.2 Device performance

FDA views an inhalation aerosol product such as the proposed epinephrine HFA to be the sum of its parts, i.e., the product entails all of the device components, the formulation, and any necessary protective packaging. In general, dose delivery is influenced not only by the device components but also by the formulation and any interactions between the formulation and the device components. Even if various device components and formulations have been found to be acceptable in other products, the same performance characteristics cannot be guaranteed for new combinations in new products. Therefore, the Agency requires an evaluation of product performance for all new MDI asthma products. Such an evaluation typically includes in vitro assessment of ruggedness and reliability, root-cause evaluation of all device complaints, and testing of a random sampling of clinical trial device units. Any device malfunctions seen in clinical trials are of concern, particularly for an asthma reliever medication, which may be used in a life-saving rescue situation. At multiple interactions with the Applicant during the development program for epinephrine HFA, the Agency advised the Applicant to include information supporting the performance of the drug-device product in the NDA.

Likewise, while dose indicators are considered a favorable addition to an MDI product, the Agency expects a demonstration of reliability and accuracy in the clinical program. In general, dose indicators are expected to have reliability as close to 100% as possible, especially with regards to undercounting.⁹ If a dose counter/indicator undercounts, the indicator will overestimate the number of remaining actuations. This is especially concerning for quick relief medications, such as epinephrine-HFA, in which the dose

⁹ FDA Guidance for Industry: Integration of Dose-Counting Mechanisms into MDI Drug Products, March 2003.

indicator may incorrectly show that there are remaining doses of medication and a patient fails to get relief of acute bronchospasm. Undercounting of dose counters/indicator for quick relief medications poses a safety concern. In contrast, overcounting is unlikely to result in lack of efficacy, but may pose an issue for patients if they are required to purchase a new MDI despite available doses.

Armstrong evaluated device performance in the Phase 3 trials. Dose indicator performance for the epinephrine-HFA and placebo arms was evaluated separately in the adult trial and safety extension, and Armstrong did not categorize dose indicator errors as a device performance issue. During the trials, patients recorded study drug use, mouthpiece cleaning, and device malfunctions in a diary. All used and unused study drug was collected during site visits, and patients were also queried regarding device malfunctions. Specific manufacturing performance evaluation tests were to be performed on all devices for which there was a malfunction reported as well as a random sample of returned MDI units. In addition, the incidence of overcounting and undercounting for the MDI dose indicators were to be evaluated, with dose indicator readings compared to patient diary reports and canister weights.

The original submission for epinephrine HFA presented summary information on device and dose indicator performance, including a summary of the root-cause analysis performed for the reported malfunctions. Armstrong concluded that the majority of reported problems were attributable to user error and inconsistent subject diary information, and the evaluation did not identify a problem inherent to the product. In response to FDA's concerns outlined in the Agency's briefing document and presentation materials for the February 25, 2014, joint Advisory Committee meeting, Armstrong submitted additional analyses of device and dose indicator performance on February 24 and March 18, 2014. Armstrong also submitted responses to information requests on April 2 and May 12, 2014. Despite the proximity to the action date, the CMC and clinical teams completely reviewed all of these additional submissions during this review cycle given the importance of this issue for approvability.

Device performance

Based on the original submission, of the 3508 MDIs that were returned during the Phase 3 trials, patients or study sites reported a malfunction with 251 (7.2%) of them. See Table 1. Of the 251 MDIs with reports of malfunction, 53 were due to clogging and 31 were not dispensing properly; specifics of the other 167 reports were not provided. Per the original submission, Armstrong stated that 243 of the devices that were reported to malfunction were within specifications, concluding that the reports were erroneous. Of the other 8 devices, one had a broken valve stem, but had been used to dispense some doses prior to breakage, and the other 7 had dose indicators that were damaged or were at zero, precluding testing.

Table 1: MDI device malfunctions reported in the Phase 3 trials (original NDA submission)

Trial	Number of used MDIs returned	Number of MDIs with reported malfunction n (%)
C (adult)	2232	116 (5.2%)
C2 (adult safety extension)	1071	109 (10.2%)
D (pediatric)	205	26 (12.7%)
Total	3508	251 (7.2%)

Source: eCTD Section 3.2.P.2.2; Performance Evaluation Report QARD-018-11-02 FR

In the February and March amendments, Armstrong provided additional information on the number and nature of malfunction reports, as well as the analyses of returned units. The following summary is taken from the review by Dr. Susan Limb, Team Leader in the Division of Pulmonary, Allergy, and Rheumatology Products.

The Applicant states that 4,249 units were returned for malfunction assessment, of which 3,752 were eligible for evaluation. A total of 495 returned units were unused and were therefore excluded from evaluation, while another 2 returned units had incomplete information and were also excluded. Based on the new submissions, the overall malfunction report rate remains 7% (251 of 3,752). Of the 3,752 returned eligible units, 61 (2%) were reported as clogging or suspected clogging and another 47 (1%) were reported as not dispensing properly or having an improper spray.

Two of the reported malfunctions which were not categorized as potential clogging/improper spray issues are worth noting. One unit (PMFU ID (b) (4)) was reported as a leakage problem, but notes from the patient interview state that the patient reported needing extra priming sprays and the absence of a spray despite cleaning and reassembling the inhaler. Another unit (PMFU ID (b) (4)), which was categorized as having an “appearance” issue due to a white film on the canister, was also noted to not be dispensing properly and required extra priming sprays.

Of the 251 reported malfunctioning units, 4 units could not be tested per the Applicant because they were empty. Three units were found to have physical damage which the Applicant attributed to user mishandling: a broken valve stem (PMFU ID (b) (4)), dose indicator separated from the canister (label appeared to be cut; PMFU ID (b) (4)), and sticky substance near the dose indicator (PMFU ID (b) (4)). Five other units had malfunctions confirmed on testing that were related to dose indicator error and are discussed separately in the following section.

Of the 251 reported malfunctioning units, a total of 245 units underwent testing for shot weight and proper dispensing and were deemed to be functioning properly on root cause analysis. The malfunction reports for these 245 units were subsequently attributed to errors in use or reporting. While the Applicant’s assessment did not identify a specific device issue, the review notes that 9 reports of clogging or improper spray appeared to resolve with extra cleaning performed by the patients. One patient reported cleaning the device 2-3 times per day due to clogging, and visual inspection of the device in the clinic revealed accumulation of medication inside the mouthpiece (PMFU ID (b) (4)). There were 22 reports of

clogging or improper spray that appeared to resolve with extra sprays performed by the patients, and 4 reports of clogging that resolved with a combination of extra cleaning and additional sprays. It is not possible to determine whether these additional actions performed by the patients may have mitigated a clogging/improper spray problem prior to testing.

Dose indicator

Dose indicator evaluations were performed for the adult Phase 3 trial and extension. In the original NDA submission, the sponsor performed the analysis of dose indicator performance using subject's e-diary reports to determine the number of doses administered. Of the 1134 samples included in the Phase 3 adult efficacy trial, 360 were excluded from the evaluation for various reasons, primarily if the e-diary count exceeded the maximum or minimum dosing puffs as calculated by canister weight. Of the evaluated samples, 30 (4%) had undercounting of more than 10% compared to the e-diary. This number was even higher in the extension trial (13%), in which fewer samples were excluded. Armstrong discounted many of these, mainly if the e-diary didn't match the number of doses calculated from canister weight. For overcounting, Armstrong used a 20% acceptance criterion. Notably, 437 samples had overcounts of less than 20% which were not analyzed. The sponsor concluded that the cases of "true" overcounting or undercounting were most likely due to patient error, including not pressing squarely on top of the dose counter, spraying 2 puffs in too rapid succession, or dropping the device.

Table 2: MDI dose counter errors assessed in the Phase 3 trials (original NDA submission)

	Trial C (adult)	Trial C2 (adult safety extension)
Number of returned MDIs included in analysis	2268	1175
Number of samples¹	1134	1175
Excluded samples	360	0
Evaluated samples	774	1175
Samples with >10% undercounting	30	149
"True undercounting"²	5	7
Samples with >20% overcounting	67	62
"True overcounting"²	3	7

Source: eCTD Section 3.2.P.2.2; Performance Evaluation Report QARD-018-11-02 FR

1= number of samples determined as the number of MDIs divided by the number dispensed per study visit

2=as determined by the sponsor, excludes samples for which the diaries did not match the number of doses as calculated by the canister weight

In the February, March, and April amendments, Armstrong provided additional analyses of dose counter performance using unit weight change to determine the number of sprays used. In this analysis 3,742 units were analyzed of a possible 4,249 returned units; units were excluded from the analysis only if they were unused (495) or were broken/lacked unit weight records (12). Based on this analysis, 51 units (1%) undercounted by 11 doses or

more and 16 units (0.4%) undercounted by 20 puffs or more. Conversely, 1078 units (29%) overcounted by 11 doses or more and 273 units (7%) overcounted by 20 puffs or more. A distribution curve showed that 232 units (6%) counted correctly (zero overcounts or undercounts).

The sponsor notes that the manufacturing process for epinephrine HFA

(b) (4)

3.3 Summary of CMC and device issues

It is unusual to have 7% of devices reported as malfunctioning during a clinical trial. Clinical trials are generally considered to be a best-case-scenario for device performance because patients receive detailed instructions for use and follow up. While the sponsor's root cause analysis of these errors did not identify a specific device defect, the high numbers of reports suggests that consumers may have difficulty using the proposed product correctly. Similarly, although the device and dose counter function acceptably when used exactly as labeled, simulation testing demonstrates that failure to follow the instructions may result in clinically significant performance issues. The complexity of steps required for shaking, priming, actuation, and cleaning may contribute to usability issues.

This usability issue is especially problematic for an OTC product because consumers will be using the device without the oversight of a health care professional who the user might call if there is a problem. Usability is even more concerning considering that this product is indicated for acute relief of asthma symptoms, which if not treated promptly may result in adverse asthma outcomes. Additional data to support consumers' ability to use epinephrine HFA in the OTC setting are needed prior to approval.

4 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

As epinephrine has a long history of use and has been previously approved as a CFC-inhalational product, no additional toxicology data are required to support the active ingredient epinephrine for inhalational use. No toxicology information was submitted in the original NDA application. Letters of authorization were provided to the DMFs for epinephrine and the HFA-124a propellant and deemed acceptable by the pharmacology/toxicology review team.

In addition to switching propellants, Armstrong made other changes to the formulation, including the addition of new excipients, polysorbate 80 and thymol. Both of these ingredients are listed in the FDA inactive ingredient database and both have been used in inhalational products. However, thymol was only used in a single inhaled product, Halothane, currently off the market in the US. Halothane is a general anesthetic used for induction and maintenance of general anesthesia—a short term use. In contrast, epinephrine HFA, while used intermittently, is considered to be for chronic use because consumers can

use it repeatedly over a lifetime. No inhalational repeat dose toxicity studies, reproductive/developmental studies, or carcinogenicity studies are currently available to FDA for thymol.

In a May 12, 2014 response to an FDA information request, Armstrong submitted the following supportive information for thymol: 1) thymol is considered generally recognized as safe (GRAS) for oral use, 2) exposure to thymol via inhalation occurs from contact with food and seasonings containing thymol, 3) exposure to thymol via epinephrine-HFA is minimal, 4) there is prior human experience with inhaled thymol in Halothane, and 5) there is prior human experience with Karvol inhalation capsules (a discontinued UK product for the common cold that does not have a lung delivery device).

The pharmacology/toxicology review team did not find any of these arguments compelling because they fail to demonstrate safe use over a chronic duration, and the team recommends a complete response action. To support approval, a repeated dose inhalation toxicity study of 6 months duration in an appropriate species demonstrating no adverse findings is needed. I concur with this recommendation. From a clinical standpoint, it is very difficult to predict long-term pulmonary safety based on oral safety. Also, chronic pulmonary changes may not result in easily identifiable symptomatology that would lead a consumer to stop the drug in a timely fashion, particularly in persons with underlying lung disease, such as asthma.

5 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

There is an extensive literature base to support the pharmacology of epinephrine and discussions may be found in many pharmacology textbooks. Epinephrine is rapidly metabolized in the systemic circulation and has a brief duration of action (3-5 minutes) when given SC or IM. It cannot be given orally, as it is rapidly metabolized by catechol-O-methyltransferase and monoamine oxidase in the wall of the gastrointestinal tract and by monoamine oxidase in the liver, with extensive first pass metabolism. Pharmacokinetics are linear.

Armstrong conducted three pharmacokinetic (PK) studies comparing the systemic exposure of epinephrine following oral inhalation of epinephrine-HFA and Primatene Mist. Due to low concentrations of epinephrine in plasma at the proposed therapeutic epinephrine-HFA dose (2 x 125 mcg/actuation) all PK studies were conducted using a dose 4 to 6 times of the proposed therapeutic dose. Of note, the exogenous epinephrine concentrations in the plasma declined to an undetectable level within an hour post-dose in all the PK studies. Overall, these trials demonstrated that the relative bioavailability of epinephrine HFA at 125 mcg/actuation was 37% higher as compared to Primatene® Mist (220 mcg/actuation) for total epinephrine. Further, the C_{max} for epinephrine HFA was 4.5 times higher than that for Primatene Mist.

6 CLINICAL MICROBIOLOGY

Product quality microbiology review found that the microbial limits specification and method for release testing is acceptable.

7 CLINICAL AND STATISTICAL—EFFICACY

Some characteristics of the relevant clinical trials are shown in Table 3. The design and conduct of these trials are briefly described below, followed by efficacy and safety findings. All trials were conducted in the United States. In general, the type of trials performed during this development program is consistent with other approved prescription bronchodilator products undergoing reformulation from CFC to HFA propellants.

Table 3: Relevant clinical trials with epinephrine HFA

Trial	Design	N	Treatments	Duration	Primary Endpoint	Number of Sites % of patients from US
<i>Year completed</i>						
Dose-ranging trials in adult asthma patients						
Trial A 2010	R, DB or EB, PC, AC, CO	26 26 26 26 26	EpiHFA 2x125 mcg/inh EpiHFA 2x160 mcg/inh EpiHFA 2x220 mcg/inh EpiHFA Placebo-HFA Primatene® 2x220 mcg/inh	Single dose	AUC of Δ%FEV1	4 100%
Trial A2 2011	R, DB or EB, PC, AC, CO	30 30 30 30 30 30 30 30	EpiHFA 1x90 mcg/inh EpiHFA 1x125 mcg/inh EpiHFA 2x90 mcg/inh EpiHFA 2x100 mcg/inh EpiHFA 2x125 mcg/inh EpiHFA Placebo-HFA Primatene® 1x220 mcg/inh Primatene® 2x220 mcg/inh	Single dose	AUC of Δ%FEV1	5 100%
Adult and adolescent efficacy and safety trials						
Trial C 2011	R, DB or EB, PC, AC, PG	248 61 64	EpiHFA 2x125 mcg/inh QID EpiHFA Placebo-HFA QID Primatene® 2x220 mcg/inh QID	12 weeks	AUC of Δ%FEV1	34 100%
Trial C2 (safety extension) 2012	R, DB or EB, PC, AC, PG	134 38 35	EpiHFA 2x125 mcg/inh QID EpiHFA Placebo-HFA QID Primatene® 2x220 mcg/inh QID	12 weeks	Safety	27 100%
Pediatric efficacy and safety trial (children ages 4-11 years)						
Trial D 2012	R, DB, PC, PG	35 35	EpiHFA 2x125 mcg/inh QID EpiHFA Placebo-HFA QID	4 weeks	AUC of Δ%FEV1	8 100%

Source: Sponsor's NDA 205-920 Submission dated July 22, 2013, Section 5.2 (Tabular Listing of All Clinical Studies), pg. 5 (Table 5.2-1)

Note: N=number in ITT population randomized

Key: AC=active-controlled, DB=double-blind, EB=evaluator blind, PC=placebo-controlled, PG=parallel group, R=randomized, EpiHFA=epinephrine HFA

5.1 Design and conduct of the trials

Dose ranging trials

Trial A was a randomized, double-blind, placebo controlled, 5-way cross-over, single dose, dose-ranging trial in 26 patients with mild to moderate asthma. For inclusion in the trial,

patients were required to have an FEV1 50-85% predicted and demonstrate airway reversibility following epinephrine-CFC administration ($\geq 15\%$ improvement). The treatment arms included a single dose of 2 inhalations of epinephrine HFA 125 mcg, 160 mcg, 220 mcg, placebo, and Primatene[®] 220 mcg. The Primatene[®] arm was evaluator blinded, and all treatments were self-administered. In each treatment period, patients received one dose of trial medication followed by PFTs at 5, 30, 60, 120, 180, 240, and 360 minutes post-dose. Between treatment periods, there was a 2- to 14-day washout period. The primary endpoint was the Area Under the Curve from 0 to 4 hours after dosing (AUC0-4) of the percent change from baseline of FEV1.

Trial A2 was a randomized, double-blind, placebo controlled, 8-way cross-over, single dose-ranging trial in 30 patients with mild to moderate asthma. Enrollment criteria were the same as Trial A. The treatment arms included a single dose of epinephrine HFA of 90, 125, 180, 200, or 250 mcg, placebo, and Primatene[®] 220 and 440 mcg. The Primatene[®] arms were evaluator blinded, and all treatments were self-administered. In each treatment period, patients received one dose of trial medication followed by pulmonary function testing (PFTs) at 5, 30, 60, 120, 180, 240, and 360 minutes post-dose. Between treatment periods, there was a 2- to 14-day washout period. The primary endpoint was the AUC of the percent change from baseline of FEV1.

Adult Phase 3

Trial C was a 12-week randomized, double-blind or evaluator-blind, placebo and active controlled, parallel-group multicenter trial to evaluate the efficacy and safety of epinephrine-HFA in approximately 250 adults and adolescents with asthma. Patients were randomized 4:1:1 to receive epinephrine-HFA (250 mcg delivered as two 125 mcg inhalations), placebo to epinephrine-HFA, or epinephrine-CFC (Primatene[®] 440 mcg delivered as two 220 mcg inhalations). Each treatment was administered 4 times daily for 12 weeks. Albuterol rescue medication was also provided. Epinephrine-HFA was double-blinded, while epinephrine-CFC was evaluator-blinded. Patients had documented stable asthma requiring an inhaled beta-agonist with or without inhaled corticosteroids (ICS) for at least 6 months, baseline FEV1 of 50-90% predicted, and at least 12% airway reversibility after inhaling 2 puffs of epinephrine-CFC. The primary endpoint was the mean area under the curve from 0-6 hours (AUC) of the % change from same-day baseline in FEV1 versus time at Week 12.

Trial C2 was a 12 week safety extension of Trial C. Patients enrolled in the extension Trial C2 were continued on the treatment to which they had been randomly assigned in Trial C. Patients in the epinephrine-CFC arm were discontinued per protocol after the sunset date for this product. There were no efficacy assessments in this trial. Safety evaluations included adverse events, vital signs, ECGs, clinical laboratory evaluations, rescue medication use, and concomitant medications.

Pediatric Phase 3

Trial D was a 4 week randomized, double-blind, placebo-controlled, parallel group trial comparing epinephrine HFA to placebo in 70 children ages 4-11 years with asthma. Epinephrine-HFA was administered at a dose of 250 mcg (two 125 mcg inhalations) 4 times daily. Patients had stable asthma requiring a beta-agonist with or without ICS,

baseline FEV1 of 50-90% predicted, and at least 12% airway reversibility after inhaling 2 puffs of epinephrine-CFC. The primary endpoint was the mean AUC of the % change from baseline in FEV1 versus time at Week 4.

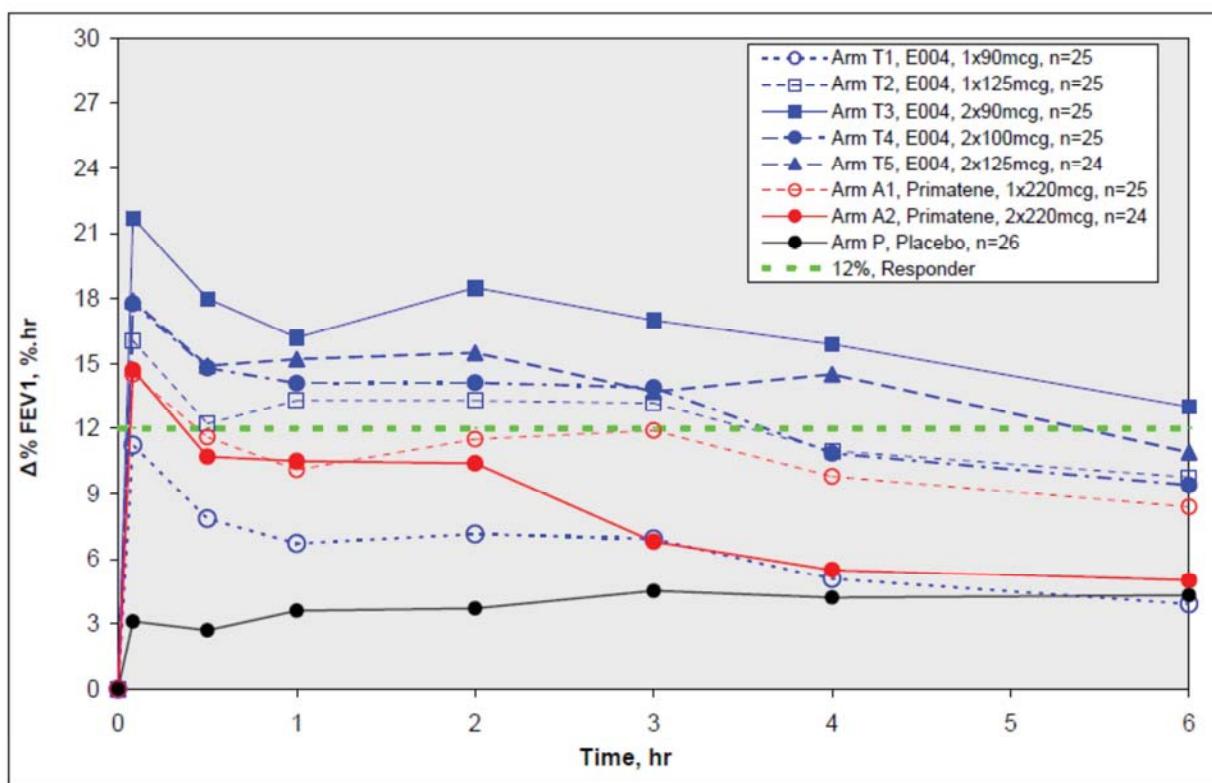
5.2 Efficacy Findings

Dose selection

Although Trial A demonstrated a statistically significant bronchodilator effect after all doses of epinephrine-HFA compared to placebo, there was no separation between doses, suggesting that the doses selected were too high. As such, the sponsor conducted a second single dose ranging trial with lower doses (Trial A2), under advisement by FDA at an End of Phase 2 meeting.

Trial A2 demonstrated dose ordering, particularly for the lower doses. In this trial, 125 mcg provided a more consistent benefit over the time period evaluated for both one and two inhalations. One inhalation of 125 mcg was the lowest dose expected to provide significant bronchodilator effect compared to placebo over the 6 hour dosing interval, with one inhalation of 90 mcg being an inferior dose. Dose ordering was less clear above 125 mcg, as the 180 mcg dose appeared to demonstrate the greatest benefit. See Figure 1. Based upon the dose ranging trials, the sponsor carried forward the 125 mcg dose for assessment of efficacy in phase 3 trials.

Figure 1: Trial A2: Percent Change FEV1 over time



Source: NDA 205,920, Module 2, Summary of Clinical Efficacy, Figure 2.7.3
E004=epinephrine HFA

Efficacy in adults

Trial C demonstrated bronchodilator efficacy of epinephrine-HFA compared to placebo for the primary endpoint, mean area under the curve (AUC) of the % change from baseline in FEV₁ versus time at Week 12, as well as a variety of secondary endpoints. See Table 4. In general, the efficacy results are comparable to those observed with epinephrine-CFC. Results were robust across a variety of different methods for handling missing data and population definitions.

Table 4: Trial C: Selected endpoints in ITT analysis

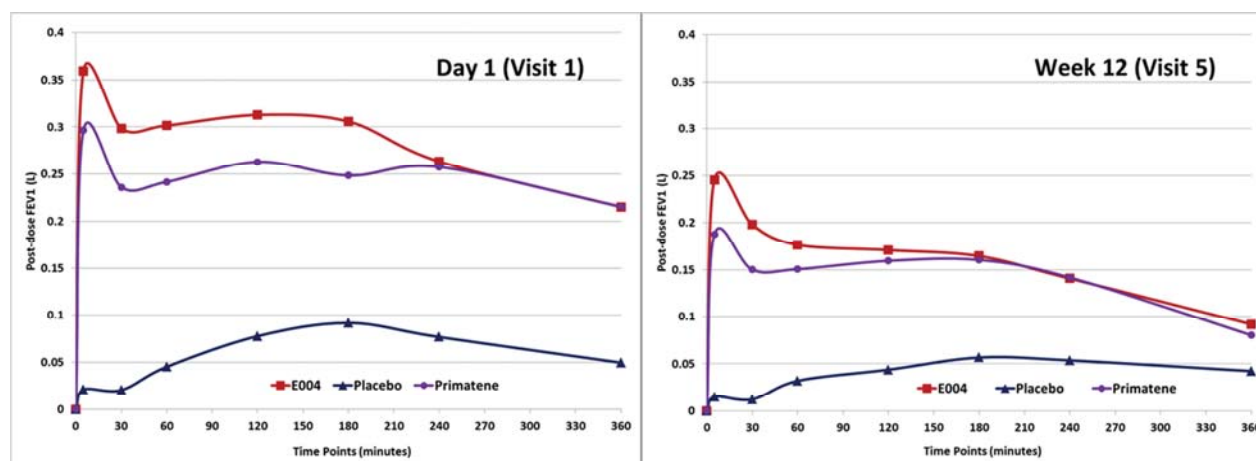
	Epi-HFA 250mcg (n=248) Mean (SD)	Placebo (n=61) Mean (SD)	Primatene 440mcg (n=64) Mean (SD)	Mean Diff. (Epi-HFA - Placebo)
AUC_{0-6hrs} of Δ%FEV₁ (%*hr)	40.59 (56.09)	12.76 (55.77)	35.67 (45.70)	27.83 (11.99, 43.68)¹
AUC _{0-6hrs} of ΔFEV ₁ (L*hr)	0.92 (1.20)	0.26 (1.32)	0.84 (1.14)	0.67 (0.30, 1.03) ¹
ΔFEV ₁ at 5 min. post-dose (L)	0.25 (0.24)	0.02 (0.14)	0.19 (0.23)	0.23 (0.184, 0.28) ¹
Fmax of FEV ₁ (L)	2.75 (0.70)	2.53 (0.60)	2.70 (0.71)	0.22 (0.041, 0.40) ¹
Time-onset (minutes)	18.2 (50.7)	99.1 (100.9)	40.1 (66.2)	-80.9 (-133.4, -28.5) ¹

Note 1: p-value <0.05. ΔFEV₁= Change from baseline (pre-dose) FEV₁; Analyses used imputation model C
The mean, standard deviations, 95% confidence interval, and p-value are based on two-sided t-test analyses.
Source: FDA statistical reviewer calculations

A total of 21 and 16 adolescent patients aged 12-17 were enrolled in the intent-to-treat and per-protocol populations, respectively. For adolescent patients, the primary analysis results also show a statistically significant difference for the primary endpoint at 12 weeks. For other subgroups, there were no treatment differences by gender, race, or severity interactions.

Compared to the first dose, tachyphylaxis was demonstrated after 12 weeks of scheduled dosing, with a mean difference from placebo in FEV₁ at 5 min (peak) of 0.34L and 0.23L on Day 1 and Week 12, respectively. Mean difference from placebo in FEV₁ at 6 hours (trough) was 0.17L on Day 1 and 0.05L on Week 12. See Figure 2.

Figure 2: Trial C: Change from baseline of FEV₁(L) at Day 1 and Week 12



Source: Calculated by FDA statistical reviewer Feng Zhou, MS

Efficacy in children

The sponsor is not seeking an indication in pediatric patients less than 12 years of age. However, because epinephrine-CFC MDI was approved in children down to 4 years of age, FDA raised the concern that consumers may use the epinephrine-HFA product in children under 12 years of age and requested that the sponsor include the available pediatric data in the NDA for completeness. Although the results of trial D showed numerical benefit of epinephrine-HFA over placebo in AUC_{0-6hr} of $\Delta\%FEV_1$ at 4 weeks, the difference was not statistically significant with a two-sided p-value of 0.125 based on the per protocol analysis. This finding was supported by the intention to treat analysis and three sensitivity analyses. Like the adult data, results showed tachyphylaxis compared to Day 1.

8 SAFETY

The pharmacologic and physiologic effects of epinephrine are well characterized, including stimulation of the sympathetic nervous system to increase heart rate and the force of heart contractions, increase blood pressure, and increase the breakdown of glycogen into glucose resulting in increased blood glucose levels. The β_2 effects of epinephrine include relaxation of bronchial smooth muscles resulting in an increase in bronchial airflow, dilation of blood vessels in skeletal muscles and the liver, release of glucose into the circulation, and inhibition of release of mediators from stimulated eosinophils, mast cells, and basophils. Safety data for epinephrine-HFA was reviewed in light of these known effects of the active moiety.

Safety in clinical trials

The safety profile in the adult Phase 3 trials does not suggest a serious safety signal, although the clinical trial database is small, with 373 adult and adolescent subjects and patients exposed to any dose of epinephrine-HFA. Of these, 248 received more than one dose of drug. In addition, 35 pediatric patients aged 4-11 received more than one dose of epinephrine-HFA.

There were no deaths, and 3 serious adverse events¹⁰ (SAEs). The two SAEs that occurred in the epinephrine-HFA group were left breast cancer in a 59 year old female that occurred 2 months after starting the drug, and pregnancy in a 33 year old female. AEs leading to discontinuation were generally balanced between the epinephrine-HFA and placebo groups as were the majority of other AEs. The most commonly reported AE was tremor, which was the one event with a notable imbalance, occurring in 10% of patients in the epinephrine-HFA group compared to 2% in the placebo and epinephrine-CFC groups. This finding is consistent with the non-selective beta-agonist effect of the drug. Other events occurring more frequently in the epinephrine-HFA group compared to control groups were throat irritation, cough, feeling jittery, bronchitis, dizziness, respiratory tract irritation, glossodynia, ligament sprain, and muscle strain. Examination of laboratory parameters did not demonstrate any changes in chemistry values, including glucose and potassium, likely to be clinically relevant.

Consumer studies

Armstrong conducted 4 consumer studies, including 3 label comprehension studies and one behavioral (human factors study) evaluating whether subjects could correctly use the device. Given the long history of use of epinephrine CFC, the development program for epinephrine HFA was designed to focus only on elements that differed from the CFC product label, and did not focus on self-selection or safety questions related to the label that are commonly evaluated as part of a de novo OTC program.

The label comprehension studies were iterative and focused on 3 primary communication objectives, all related to the dose indicator: keep track of the number of sprays if the inhaler is dropped, replace the inhaler if the dose indicator reads zero, and if the dose indicator reads zero the correct dose in each spray is not assured. Secondary objectives included cleaning the mouthpiece daily and priming. The reported final results (third study) were 87% (lower bound of the 95% confidence interval 83%), 93% (LB 90%), and 93% (LB 90%) correct, respectively, for the primary objectives in a population containing only normal literacy subjects. Low literacy subjects did considerably worse and were not included in the overall cohort. In addition, the label comprehension studies identified limitations in consumers' understanding of the following critical information: the need to prime the inhaler before using the first time, the need to clean the product daily after use, and the need to reprime when wet.

The FDA social science reviewer noted a number of methodological concerns with the label comprehension studies, including that they failed to completely assess all of the knowledge required to successfully use the device. Of clinical interest, the additional questions evaluating use in mild asthma, the asthma alert for worsening symptoms, and cardiovascular risk factors scored very poorly (67-75% in normal literacy, 39-46% in low

¹⁰ Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

literacy), suggesting that consumers may not completely understand the epinephrine label despite the product being on the market for many years with a similar label.

A behavioral study was performed to assess those steps in the proposed consumer package insert regarding priming, cleaning and medicating that are different from epinephrine-CFC. Of the 61 subjects, 8 were former Primatene[®] Mist users, 19 were asthma sufferers, 10 were ages 12-17, and 5 were low literacy. Placebo was utilized instead of active ingredient for the purposes of this study. The behavioral study also had methodological issues, the most concerning of which was that the study did not assess whether consumers understood the initial priming and cleaning of the product without prompting. It was difficult to assess whether cleaning of the device was performed appropriately as some subjects had difficulty demonstrating the cleaning steps without a sink. Especially given the population likely to use this product, subjects with low literacy were inadequately represented (5/61, 8%).

In the behavioral study, performance in several key areas that could impact device performance were noted, with only 74% of subjects shaking the MDI prior to priming, 82% priming prior to use, 64% correctly washing the mouthpiece through the top opening, and 74% shaking the MDI prior to use. Some consumers had difficulty removing the canister to clean the product, and the study did not assess whether consumers correctly reassembled the product after cleaning. Incorrectly completing these steps could cause dose variability and clogging with resulting failure to deliver the appropriate dose, a potential issue for both safety and efficacy.

These results in label comprehension and behavioral studies are extremely concerning that consumers will be unable to appropriately use the device in an OTC setting, especially given the number of device issues reported during the clinical trial under medical supervision.

Post-marketing data

Post-marketing safety data from epinephrine-CFC were reviewed from the following sources: the sponsor's pharmacovigilance database, FDA's Adverse Event Reporting System (FAERS), the American Association of Poison Control Centers' National Poison Data System (NPDS), and the published literature. All of these sources are subject to a number of limitations, primarily due to issues inherent in spontaneous reporting. Overall, a comparatively small number of adverse events were identified from these sources relative to the distribution of the product, suggesting that the product was used safely in the majority of consumers. Given differences between the products, extrapolation of post-marketing safety from the CFC product to the proposed HFA product must be undertaken with caution.

In the sponsor's pharmacovigilance database, there were 110 unique cases, including 3 deaths and 30 cases with SAEs. Of the 3 deaths, 2 apparently started with respiratory adverse events; the 3rd was unknown. Very limited details are available. The most frequently reported SAEs were dyspnea/asthma, tachycardia, drug dependence, and cardiac arrest/myocardial infarction. In addition, 7 cases had SAEs of "drug ineffectiveness", and there were 2 reports of drug overuse/misuse related to cardiac adverse events. The most frequent non-serious AEs were drug ineffective, product taste abnormal, throat irritation, dyspnea/asthma, breath alcohol test positive, and chest pain/discomfort.

From 1997-2012 there were 389 AEs identified in the FAERS database. The sponsor reports that there were 66 million units of Primatene[®] distributed during this time period. Review revealed a similar distribution of reported events; the most frequent were: drug ineffective, drug abuse, dyspnea, drug dependence, and asthma. Of these events, there were 116 SAES, including 41 deaths. Given limited information and various confounding factors, causality could not clearly be determined for these deaths. Twelve deaths included cardiac-related AEs, and 5 were related to abuse/misuse of the product. Twenty-five reports included adverse events occurring in children. Similar to reports described in adults, most were related to ineffectiveness, asthma symptoms, palpitations and chest discomfort. There were 2 deaths reported in children, one in a 10 year old boy who seized while in a pool, and one in a 17 year old female who died of an asthma exacerbation.

The NPDS from 2008-2012 included a single case of seizure and stroke in a 28 year old female after 30 doses of epinephrine-CFC. Limited case reports were also found in the literature, most related to cases of misuse/overuse. One small (N=8) open label cross over study¹¹ comparing albuterol to epinephrine in nocturnal asthma concluded that epinephrine-CFC has a similar safety and efficacy profile to albuterol, with less tachycardia and hypokalemia than albuterol at higher than recommended doses. There was also a review article¹² of post-marketing reports of safety identifying 13 deaths from 1975 to 1997 and analyzing survey data of OTC epinephrine use. The authors concluded that the occasional use of OTC epinephrine inhalers appears to be safe and effective when used according to labeled instructions, but raised concern about abuse/misuse and use of OTC epinephrine in patients with persistent asthma. This review formed the basis of the American Medical Society 1999 policy on OTC epinephrine inhalers recommending: 1) to strengthen labeling to better educate users about inappropriate use, 2) to encourage FDA to re-examine whether OTC epinephrine inhalers should be removed from the market, and 3) to evaluate whether OTC product availability is a risk factor for serious asthma-related outcomes.

Cardiac safety

Cardiac safety of epinephrine was also reviewed by the Division of Cardiovascular and Renal Products at FDA. In clinical trials of epinephrine-HFA, there were no serious AEs related to cardiac events although numbers were too small to rule out significant effects on cardiac outcomes. Non-serious adverse events relevant to cardiac safety that occurred more frequently in the epinephrine groups compared to placebo were chest pain, hypertension, tachycardia, and palpitations, although narratives of the chest discomfort/pain events suggest that they were related to asthma rather than cardiac ischemia. See Table 5.

¹¹ Hendeles L, PL Marshik, R Ahrens, Y Kifle, J Shuster. Response to Nonprescription Epinephrine Inhaler During Nocturnal Asthma, *Ann Allergy Asthma Immunol*; 2005, 95:530-534.

¹² Dickinson BD, RD Altman, SD Deitchman, HC Champion for Council on Scientific Affairs, American Medical Association. Safety of Over-the-counter Inhalers for Asthma; *CHEST*, 2000, 118:522-526.

Table 5: Non-serious adverse events relevant to cardiac safety in adult Phase 3 trials (Trial C and C2 combined)

	Placebo N=61 n (%)	Epinephrine HFA N=248 n (%)	Primatene® N=64 n (%)
Chest discomfort	1 (2)	9 (4)	1 (2)
Chest pain	0	3 (1)	0
Tachycardia	0	1 (0.4)	0
Heart rate increase	0	1 (0.4)	0
QTc prolongation	0	0	0

Source: Sponsor's NDA 205-920 Submission dated December 20, 2013, Section 1.2 (Cover Letters), pg. 10-12 (Table ISS-23U)

Note: N=Number of patients in the Treated Population

Review of vital signs and ECGs from clinical trials using the proposed dose of 250 mcg (two 125 mcg inhalations) demonstrates minimal changes, although noise in the data could potentially obscure larger changes in some patients. The high dose PK study in healthy volunteers demonstrated substantial increases in blood pressure (>50 mmHg systolic) and pulse (>60 bpm) in some patients 10 minutes after a single dose of 1250 mcg and 1600 mcg, although the median increases were more modest (pulse increase of 5-6 beats, systolic blood pressure increase of 9-14 mmHg, diastolic blood pressure increase of 1-3 mmHg). To achieve a dose of 1250 mcg, a patient would have to take 10 inhalations of the proposed 125 mcg dose in rapid succession; a dose of 1600 mcg would require 12-13 inhalations. These results are relevant for use beyond the labeled dose, although they provide some degree of reassurance that the proposed dosing is appropriate to minimize these effects.

Post-marketing reports of adverse events with epinephrine-CFC in both the literature and the FDA AERS database do not demonstrate a significant cardiovascular signal. In addition, FDA analysis of the AERS database using data mining techniques does not demonstrate a signal for serious cardiac AEs.

Differences between epinephrine-HFA and Primatene Mist®

Apart from the obvious differences in propellant and inhaler design, a number of differences exist between the epinephrine-HFA and the previously-marketed epinephrine-CFC product. It is likely that consumers who previously used and are familiar with the CFC product will also use the epinephrine-HFA product. As such, it is possible that confusion may occur for patients purchasing the product in the OTC setting without assistance of a healthcare intermediary.

- The formulation for epinephrine-HFA is a suspension rather than a solution as for the CFC product. As such, the MDI must be shaken prior to use to prevent settling. If the MDI is not shaken, this could potentially result in dose variability leading to higher doses administered.
- Epinephrine-HFA must be cleaned daily to prevent clogging. In contrast, because CFC propellants also function as cleaning agents, daily cleaning was not required for epinephrine-CFC.

- Epinephrine-HFA must be primed prior to first use, if not used in more than 2 days, if still wet after cleaning, and if dropped. Priming was not required for epinephrine-CFC.
- Epinephrine-HFA contains a dose counter whereas the epinephrine-CFC product had a transparent glass reservoir allowing patients to visually determine when the drug solution was running out.
- The proposed population for epinephrine-HFA is adults and adolescents age 12 and older, while the CFC product was approved down to age 4.
- Pharmacokinetic studies demonstrate that there are greater systemic blood levels with epinephrine-HFA compared to epinephrine-CFC. In particular, the C_{\max} is 4.5 times higher.
- The dosing instructions for epinephrine-HFA are different from the CFC product. The proposed dosing for epinephrine-HFA is one to two inhalations per dose not more often than, and not to exceed 8 inhalations in 24 hours. Dosing for epinephrine-CFC was one or two inhalations every 3 hours with no maximum.
- The sponsor notes the following advantages of epinephrine-HFA compared to the CFC product: 1) elimination of the CFC propellant to meet the requirements of the Montreal Protocol, 2) proposed dose is reduced by 43% with similar efficacy, 3) the pH of the new formulation is neutral rather than acidic, 4) amount of alcohol in the formulation (b) (4) which can reduce false positive Breathalyzer tests, and 5) an aluminum canister replaces the glass bottle.

9 ADVISORY COMMITTEE MEETING

The Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on February 25, 2014 at the FDA White Oak Campus. The purpose of the Joint NDAC/PADAC meeting was to discuss the adequacy of the efficacy and safety data submitted by Armstrong to support the approval of epinephrine-HFA at a dose of 125 mcg/actuation for the OTC use for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. The major issues discussed at the AC meeting were: a) whether the efficacy data provide substantial evidence for the use of epinephrine in the OTC setting, b) whether the safety data support use of epinephrine-HFA in the OTC setting, c) the device performance of epinephrine-HFA, and d) the proposed Drug Facts label for epinephrine.

The majority of the committee did not agree that the risk/benefit profile of epinephrine inhalation aerosol 125 mcg per actuation supported OTC use for the temporary relief of mild symptoms of intermittent asthma. The vote was 6 yes, 18 no, and 1 no vote. Committee members voted “No” primarily due to safety concerns, including: a lack of long-term safety data, limited data on use by adolescents 12-18 years of age, the device and dose indicator have issues that could impact safe use, consumers’ inability to adequately assess the severity of their asthma, the need for a learned intermediary to adequately educate asthma patients about their diagnosis, and national guidelines recommending against use of epinephrine for the treatment of asthma. A few panel members expressed

concerns regarding the device (e.g., to include an accurate, robust dose counter). Others said to avoid calling it “Primatene” to encourage consumers to read the labeling. Some members suggested that the high number of actuations per inhaler could encourage chronic use and delay health care provider visits.

On March 2, 2014, Armstrong submitted a letter outlining concerns regarding the February 25, 2014 Joint AC meeting. In it, the sponsor stated that a “gross distortion of Sponsor’s data occurred for the portion of device evaluation” in the FDA presentations and requested a “formal investigation” into the matter. Investigation of this concern showed that FDA used only the data provided in the NDA submission about device and dose indicator function. Annotated slides outlining the sources for data in the presentation of concern are included in a review by Dr. Susan Limb, DPARP. A source of the sponsor’s confusion appears to be that Armstrong’s analysis identified user error as a potential cause for the reports of malfunction, which could therefore be discounted. However, usability issues are a significant concern for an OTC inhaler product used to treat acute asthma symptoms due to the potential for adverse asthma outcomes if a dose is not delivered when needed. Another area of perception difference was that the sponsor used the dose counter analysis based on canister weight submitted on February 24, 2014 and their proposed cut off values. FDA presented the dose counter analysis using diary data submitted in the original NDA submission and included all units with demonstrated miscounting, rather than specific cut off values.

10 PEDIATRICS

As noted in Section 7, pediatric patients aged 12 and above were included in the adult asthma trials performed to support efficacy and safety of this application. A 4 week efficacy trial in pediatric patients aged 4-11 years was conducted, but was underpowered and failed to demonstrate statistically significant efficacy. As such, Armstrong is not currently seeking an indication in children aged 4-11 years. Another efficacy trial in children aged 4-11 years is ongoing. The previously marketed epinephrine CFC formulation was approved down to age 4.

This application triggers the Pediatric Research Equity Act (PREA) as a new dosing regimen and was presented to the Pediatric Review Committee (PeRC) on April 30, 2014. Because inhaled products for asthma require a device component and a new device component cannot be required under PREA, the PeRC agreed with a waiver for patients aged birth to less than 4 years of age. There was considerable discussion regarding the appropriateness of OTC availability of asthma products for pediatric patients, and the PeRC generally agreed with concerns raised by the Advisory Committee regarding the need for a learned intermediary to diagnose and treat asthma in children. However, given the specific case of epinephrine and its long history of use in the OTC setting, (b) (4)

PeRC also agreed with the recommendation of the Division that the product has already been adequately assessed for pediatric patients aged 12 to 17 years.

11 OTHER RELEVANT REGULATORY ISSUES

11.1 OSI Audits

The Office of Scientific Investigations was consulted to conduct site inspections for Trial C, the primary efficacy trial in this application. Two sites were inspected that were chosen due to high enrollment, large percentage of dropouts, and a large effect size. Both sites received a No Action Indicated (NAI) recommendation. In addition, OSI conducted an inspection of the sponsor site, and determined that the sponsor adhered to applicable GCP standards.

11.2 Financial Disclosure

The sponsor reported no significant financial interests for any investigator in the clinical trials.

11.2 Environmental Assessment

The sponsor requested an exemption to environmental assessment because this product contains the same active ingredient in a lower amount than was previously marketed product. In addition, consistent with the Montreal Protocol, this product removes CFC propellants that are known to be ozone depleting substances.

12 LABELING

12.1 Proprietary name

The sponsor proposed the proprietary names (b) (4) (December 12, 2013) and (b) (4) (April 16, 2014). Members of the Advisory Committee raised the concern that a name, that uses the same root name Primatene as the CFC formulation, known as Primatene Mist, could lead to consumer confusion and increase user error with the device due to the large number of differences between the products. This concern was echoed by the social science and clinical OTC teams.

12.1 Consumer labeling

Given the Complete Response Action, a full labeling review was not conducted. Given the issues identified with consumer understanding of how to use the device, labeling changes and additional label comprehension studies will be needed to support approval. In addition, the Complete Response letter will include an additional comment recommending “do not use” language for children under the age of 12.

13 DECISION/ACTION/BENEFIT RISK ASSESSMENT

13.1 Regulatory action

Armstrong has not submitted adequate data to support approval of epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA), at a dose of 125 mcg/actuation for over the counter (OTC) use for the temporary relief of mild symptoms of intermittent asthma in

adults and children 12 years of age and older. There are deficiencies in three discipline areas:

- Product Quality

Compliance has issued a withhold action for the drug substance manufacturing site (b) (4) which must be resolved prior to approval.

- Nonclinical

The application fails to provide data to support the long-term safety of the new excipient, thymol. Although this ingredient is considered GRAS for oral use, it has only been approved in one inhalational product, Halothane, which is an anesthetic for short-term use. To support the safety of this excipient in a chronically administered inhalational product, a 6 month inhalational toxicology study in a relevant species is needed.

- Clinical

The data from patient diaries and assessment of device and dose indicator performance in clinical trials indicate that consumers may have difficulty using the proposed product correctly resulting in perceived device malfunctions. The data from the behavioral study do not provide assurance that consumers clearly understand how to use epinephrine HFA, and label comprehension studies also identified limitations in consumer's understanding of critical elements for use. Although the device and dose counter function acceptably when used exactly as labeled, simulation testing demonstrates that failure to follow the instructions may result in clinically significant performance issues. The complexity of steps required for shaking, priming, actuation, and cleaning may contribute to usability issues. Additional data to support consumers' ability to use epinephrine HFA in the OTC setting are needed, including revised labeling, behavioral studies, and an actual use study. Depending on the results of these studies, modification of the product may be necessary to minimize user error.

13.2 Risk Benefit assessment

The overall risk-benefit assessment does not support OTC approval of epinephrine HFA for the temporary relief of mild symptoms of intermittent asthma. The major issue of concern is consumers' ability to use the product correctly in the OTC setting. This usability issue is especially problematic for an OTC product because consumers will be using the device without the oversight of a health care professional who the user might call if there is a problem. Usability is even more concerning considering that this product is indicated for acute relief of asthma symptoms, which if not treated promptly may result in adverse asthma outcomes, including hospitalization and death. In addition to the safety and efficacy risks associated with usability of the device in the OTC setting, product quality concerns due to the withhold recommendation for the drug substance manufacturing site and safety concerns due to lack of data supporting thymol as an excipient for chronic inhalational use do not support a favorable risk-benefit assessment for the product.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

13.4. Recommendation for other Postmarketing Requirements and Commitments

None due to Complete Response action.

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05/22/2014