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

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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, tachphylaxis 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.

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Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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.	• 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.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• 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).	• 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	• 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 tachphylaxis 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).	• 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.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• 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.	• 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	• 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 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	• 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.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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. • 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 heath 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.

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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 beta$_2$-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

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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 evolving[1]. The NHLBI National Asthma Education and Prevention Program (NAEPP) Guidelines classification of asthma[2], 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

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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 341.1 6 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

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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, 2011[3].

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.

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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 [redacted] drug substance is manufactured at a [redacted] facility in [redacted] The drug substance is [redacted] The drug substance produced by [redacted] The DMF [redacted] 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, [redacted], 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, [redacted] has ceased manufacture of epinephrine as of December 2017, but maintains an active DMF [redacted] 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 [redacted] for manufacture of drug product [redacted] In addition, the applicant committed to [redacted] 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 [redacted] metering valve (Model [redacted] 50 µl metering [redacted], a top mounted dose indicator [redacted] Part No. [redacted], and an orange L-shaped actuator [redacted] with a red dust cap (see Figure 1). The canister contains a [redacted] suspension of epinephrine in propellant HFA-134a, ethanol, thymol [redacted] and polysorbate 80 [redacted] 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.

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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

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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

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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

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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

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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

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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.

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- 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 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

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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 heath 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:

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- 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 [redacted] (b) (4) (December 12, 2013) and [redacted] (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, [redacted] (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.

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Figure 2: Actuator label

In this cycle, the sponsor proposed eliminating (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,

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tachphylaxis 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)

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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