Cross-Discipline Team Leader Review

Date	October 24, 2018
From	Jenny L. Kelty, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	205920, SDN-73
Applicant	Armstrong Pharmaceuticals, Inc.
Date of Submission	May 7, 2018 (Class 2 Resubmission)
PDUFA Goal Date	November 7, 2018
Proposed Proprietary Name	Primatene Mist
Established or Proper Name	Epinephrine Inhalation Aerosol
Dosage Form(s) / Route of Administration / Strength	Aerosol, metered / Inhalation / 125 mcg per actuation
Applicant Proposed Indication(s)/ Population(s)	Temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older
Applicant Proposed Dosing Regimen(s)	1 to 2 inhalations every 4 hours as needed; not to exceed 8 inhalations in 24 hours
Recommendation on Regulatory Action	Approval
Recommended Indication(s) / Population(s) (if applicable)	Temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older
Recommended Dosing Regimen(s) (if applicable)	1 to 2 inhalations every 4 hours as needed; not to exceed 8 inhalations in 24 hours

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

I recommend approval of the over-the-counter (OTC) marketing of epinephrine inhalation aerosol with hydrofluoroalkane propellant in a metered dose inhaler (epinephrine HFA), at a dose of 125 mcg per actuation for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. Armstrong has adequately addressed the deficiencies raised in the three cycle reviews. Armstrong has adequately demonstrated that consumers can use the drug device product safely and effectively without the intervention of a health care professional.

The overall benefit-risk assessment supports the approval of epinephrine HFA in the OTC setting. The potential benefits of this drug device product are related to the availability of a short-acting bronchodilator for OTC use. OTC Epinephrine HFA provides a temporary option for patients with intermittent asthma to self-treat their mild asthma symptoms without a prescription or doctor's visit when their prescription rescue inhaler runs out or is unavailable. A major issue of concern during the three cycles of reviews for the NDA, was the correct use of the product in the OTC setting. It is critical that consumers can use the inhaler safely and effectively, because delayed or inadequate treatment of acute asthma symptoms may result in serious adverse events. While it is recognized that it may not be possible to eliminate use errors, Armstrong has adequately addressed and mitigated the identified errors that may significantly impact the safe and effective use of the product in the OTC setting. The human factors (G4) validation study adequately demonstrated that the intended user population can use the proposed product safely and effectively.

The proposed indication for epinephrine HFA is for the "temporary relief of mild symptoms of intermittent asthma." Because this is the same indication as the predicate product Primatene® Mist and other oral dosage forms of bronchodilators marketed under the final monograph for Cold, Cough, Allergy, Bronchodilator, Antiasthmatic Drug Products (21 CFR 341), Armstrong did not conduct consumer behavior studies to test the consumers' understanding of this particular statement or test for the appropriate self-selection of the product for use by its intended population. According to the proposed DFL, the intended population are consumers who have been diagnosed with asthma by a physician, have intermittent asthma, and have mild symptoms. However, thorough reviews of the safety data during the first cyle review for this NDA, that included safety data from the clinical efficacy and safety trials, including cardiovascular safety from high dose pharmacokinetic trials, and postmarketing data spanning 15 years concluded that the data were supportive of the safety of epinephrine inhalation aerosol in the OTC setting.

Because of the complexities of the diagnosis and management of asthma and the potential life-threatening consequences, all patients with asthma should be under the care of a health care provider. Epinephrine HFA is not intended as an alternative to the care of a health care provider for the management of asthma or to replace any component of a prescribed regimen of therapy. The product container size was considered in the safety review because of concerns that the large number of actuations in the proposed inhaler could encourage chronic use and delay health care provider visits. The proposed epinephrine HFA contains 160 sprays per inhaler and, when used as directed, is expected to provide 80 usable doses and 80 priming sprays. Therefore, each inhaler contains 10 days of usable inhalations (maximum of 8 inhalations per day), and this was considered acceptable. If Armstrong is interested in marketing other package configurations in the future (e.g., immediate containers containing greater than 160 metered sprays, package sizes containing more than one inhaler), then DNDP expects submission of a prior approval supplement that includes justification of why larger package sizes will not

adversely impact the safety of the product.

Please refer to the benefit-risk assessment in the Division Director Review by Dr. Theresa Michele dated May 22, 2014 and December 23, 2016 and the CDTL Review by Francis Becker, MD dated December 9, 2016.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In the United States, asthma affects more than 22 million people. • Asthma is a complex respiratory disorder characterized by variable and recurrent symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying airway inflammation. The appropriate diagnosis, trigger and symptom management and treatment of asthma require the involvement of health care professionals. • The clinical manifestations of asthma are varying and recurring episodes of cough, wheeze, shortness of breath, and chest tightness. • The proposed indication is for the "temporary relief of mild symptoms of intermittent asthma." The National Asthma Education and Prevention Program (NAEPP) expert panel[1] defines intermittent asthma as symptoms that occur two or fewer days per week, nighttime awakening two or fewer times per month, use of a short-acting beta agonist for symptoms control two or fewer days per week, have no interference of normal activity by asthma symptoms, have normal baseline function, and experience one or fewer exacerbations per year. However, it is important to note that because of the complex nature of asthma, patients with intermittent asthma may experience severe exacerbations.	The proposed product is replacing Primatene Mist, which was marketed for 40 years in the over-the-counter (OTC) setting without significant clinical safety issues. The proposed indication is for "the temporary relief of mild symptoms of intermittent asthma" in adults and children 12 years of age and older." The intended use of this product is to treat mild symptoms of asthma in consumers who have been diagnosed by a physician with intermittent asthma. The Drug Facts label (DFL) contains a warning "Do not use unless a doctor said you have asthma." The DFL also contains an Asthma Warning that includes signs and symptoms of worsening asthma. The indication and warnings are consistent with the previously marketed epinephrine utilizing chlorofluorocarbon propellant (CFC) product, Primatene Mist epinephrine aerosol. This indication and warning are also consistent with the requirements for the labeling of epinephrine as a bronchodilator active ingredient in the final monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (21 CFR 341).

[1] Busse, W, Panel Chair, 2007, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (http://www.nhlbi.nih.gov/guidelines/asthma/index.htm; accessed October 20, 2018)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Epinephrine inhalation aerosol with chlorofluorocarbons as propellant (epinephrine CFC) was marketed OTC for over 40 years as Primatene® Mist without significant safety concerns. It was removed from distribution in 2011 in compliance with the Montreal Protocol on Substances that Deplete the Ozone Layer that banned CFC use around the world to protect the environment. • Medications for asthma treatment are categorized into two classes: quick relief medications (rescue) to treat acute symptoms and exacerbations and longterm medications to achieve and maintain control of persistent asthma (maintenance). • Inhaled short-acting beta2 agonists (albuterol, levalbuterol, pirbuterol) are used for quick relief of bronchospasm and are the mainstay of therapy for acute treatment. Inhaled SABAs are currently available by prescription only. • The NAEPP expert panel recommends avoidance of nonselective beta agonists (i.e., epinephrine, isoproterenol, metaproterenol) due to their potential for cardiac stimulation, especially in high doses. • Oral dosage forms containing ephedrine hydrochloride and ephedrine sulfate as bronchodilator active ingredients are marketed OTC for "temporary relief of mild symptoms of intermittent asthma" under the final monograph for Cold, Cough, Allergy, Bronchodilator, Antiasthmatic Drug Products (21 CFR 341). Epinephrine and racepinephrine hydrochloride aqueous solutions in a hand held rubber bulb nebulizer are also included as bronchodilator active ingredients in the OTC monograph. However, note that whether the hand held rubber bulb nebulizer continues to be appropriate for OTC asthma management was the subject of a Joint Advisory Committee meeting held on February 26, 2014.	If approved, Primatene Mist would be the only short acting bronchodilator inhaler available without a prescription for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older.
Benefit	• Clinical efficacy trials were conducted by the Sponsor, and the results were reviewed during the first cycle review and provided clear evidence of the proposed product's efficacy as a bronchodilator at the proposed dose.	The efficacy of Primatene Mist for the proposed indication has been adequately demonstrated during previous review cycles.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Bronchodilation demonstrated within 1 to 5 minutes after administration. • Clinical pharmacology studies reviewed during the first cycle review demonstrated that the proposed drug is minimally absorbed.	The proposed product provides a temporary option for patients with intermittent asthma to self-treat their mild asthma symptoms without a prescription or doctor's visit.
Risk and Risk Management	• No additional safety data were submitted in this resubmission. Safety data reviewed during the first cycle review that included safety data from the clinical efficacy and safety trials, including cardiovascular safety from high dose pharmacokinetic trials, and postmarketing data spanning 15 years concluded that the data, were supportive of the safety of epinephrine inhalation aerosol in the OTC setting. • In one trial, several pharmacodynamic safety measures indicated that the resultant drug levels at doses nearly 13-fold higher than proposed (125 mcg versus 1600 mcg) were not likely associated with significant safety issues of concern (transient hyperglycemia, hypokalemia, increases in blood pressure or heart rate, or arrhythmias). • Although Primatene Mist is indicated for temporary relief of mild symptoms of intermittent asthma, patients with mild asthma can have severe exacerbations with life-threatening consequences. Therefore, the device performance needs to be reliable given the proposed use as a rescue inhaler in the asthmatic population. And consumers need to understand and use the labeling for safe and effective use of the proposed product in the OTC setting. • The bench studies indicated that incorrect use of the proposed product may result in underdosing or supratherapeutic dosing. • In a 20 day simulated use study in which inhalers were used without cleaning, the data indicated that the use of inhalers beyond 7 days without cleaning resulted in the delivery of inconsistent dose.	Information reviewed in the previous review cycles for the device and dose indicator showed reliable performance over the lifespan of the product. Based on the results of the submitted bench studies, the review team agreed that the most conservative directions for use by shaking then spraying into the air prior to each inhaled dose and washing after every day of use was supported by the bench data and would result in the most consistent dose administered to the consumer. Repriming every day of use is appropriate because there exists a probability of underdosing if the inhaler is not reprimed after 24 hours. (b) (4) [redacted] Incorrect use of the proposed product may result in underdosing or supratherapeutic dosing. If users receive a supratherapeutic dose because they did not use the product correctly, they will receive an efficacious dose and will not be at risk for cardiovascular or other serious adverse events. The resultant drug levels at doses nearly 13-fold higher than proposed were not likely associated with significant safety concerns. For underdosing concerns, consumers are instructed to repeat a dose or seek medical attention if symptoms persist.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The bench study (E004 User Error Risk Report C) evaluating the emitted dose of the inhaler when it is not shaken prior to each dose during the container life (160 sprays) showed that the risk of receiving an underdose (less than (b) (4) % LC) from the inhaler is as much as 29% (108 of 368 data points) and the risk of receiving a supratherapeutic dose (greater than (b) (4) % LC) is 9%. Therefore, shaking the inhaler prior to use is a critical step. • The bench study (Supplemental Report for Risk Evaluation Due to User Errors of "No Initial Priming" or "Deviated Initial Priming") evaluating when the inhaler is not primed, indicated that 26 out of 28 dose content uniformity (DCU) data points for the first two sprays were less than (b) (4) % of the labeled content (LC). The probability for the first dose to be an underdose is 86.7%. There were 2 out of 28 data points that were between (b) (4) % LC and considered to be an overdose. None of the data points for the third and fourth sprays were out of the range of (b) (4) %. • After 1 shake and spray, the mean dose content was 84 ± 14% (range (b) (4) %). The frequency of underdosing was 86.7% and the frequency of overdosing was 6.7%. The other deviations in priming (2 shakes and 2 sprays, 3 shakes and 3 sprays, 1 shake and 4 to 5 sprays in 2 to 15 minutes, and 1 shake and 4 sprays in 30 minutes) resulted in acceptable dose content • Data from the original 1 week repriming study (Summary Report of Product Characterization Studies for Epinephrine HFA MDI) indicated that after 24 hours of rest time, the probability for the first spray dispensed from the inhaler to be an underdose (< (b) (4) %) is 3%. • Dr. Muthukumar Ramaswamy analyzed the data from the 20 day simulated use repriming study and concluded that after 2 days of non-use, underdosing is likely to occur with the first spray. However, results for the first 2 sprays (averaged) indicated that inhalers used in the study dispensed acceptable dose without reprime for up to 14 days.	The proposed labeling also advises users to see a doctor if not better in 20 minutes, get worse, need more than 8 inhalations in 24 hours, or have more than 2 asthma attacks in a week. If consumers do not follow the warnings to seek medical attention as advised in the label, then this may lead to uncontrolled asthma and more severe asthma symptoms. The human factors G4 study demonstrated the intended user population can use the proposed product safely and effectively. While it may not be possible to eliminate use errors, Armstrong has adequately addressed and mitigated the identified errors that may significantly impact the safe and effective use of the product in the OTC setting. During the 2014 Joint Advisory Committee Meeting discussions, several members of the committee raised concerns that a high number of actuations per inhaler could encourage chronic use and delay health care provider visits. DNDP advised Armstrong that if Armstrong is interested in marketing other package configurations in the future (e.g., immediate containers containing greater than 160 metered sprays, package sizes containing more than one inhaler), DNDP expects submission of a prior approval supplement that includes justification of why larger package sizes will not adversely impact the safety of the product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• It is important to have adequate labeling for consumers to use the product safely and effectively without the guidance of a healthcare professional in the OTC setting. Of concern are consumers with low literacy and consumers who are familiar with the use of the previously marketed Primatene Mist formulation or another type of inhaler who may use the new Primatene Mist inhaler incorrectly. The HF validation (G4) study results demonstrated that the intended user population can use the proposed product safely and effectively. • Beacause the labeling warnings have not been tested in consumer studies, comprehension of these warnings is not known. It is also unclear if users will recognize when their symptoms are not mild, if they are getting worse or not better, and see a doctor as recommended. Also, the consumer's understanding of the term "intermittent asthma" has not been tested.	

2. Background

Armstrong Pharmaceuticals, Inc (Armstrong) resubmitted this NDA 505(b)(2) supplement on May 7, 2018 for the third cycle review (second resubmission) and is seeking approval for the over-the-counter (OTC) marketing of epinephrine inhalation aerosol with hydrofluoroalkane propellant in a metered dose inhaler (epinephrine HFA), at a dose of 125 mcg/actuation for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. This Class 2 resubmission is a complete response to address the deficiencies identified during the second cycle review and Complete Response action on December 23, 2016. This Cross-Discipline Team Leader (CDTL) Review focuses on the issues relevant to the Complete Response and other issues reviewed during the third cycle review. This review will not address issues that were reviewed and satisfactorily resolved in the previous two review cycles and summarized in the Division Director Memos by Theresa Michele, MD dated May 22, 2014 and December 23, 2016 and the CDTL Review by Francis Becker, MD dated December 9, 2016. Please also refer to the Clinical Reviews by Ryan Raffaelli, MD dated April 15, 2014 and December 19, 2016.

In this resubmission, Armstrong submitted data from human factors validation (G4) study and additional supportive bench study data for review in support of its NDA for marketing of epinephrine HFA.

Source of CDTL Review Information
This review is written from the following primary FDA reviews in Table 1 below.

Table 1 Primary reviews for the second resubmission reflected in this CDTL review

Materials Reviewed	***Date of Review***	***Name of Discipline Primary Reviewer***
DMEPA Human Factors and Name Review	October 19, 2018	Grace P. Jones, PharmD, BCPS
DNDP Labeling Review	October 15, 2018	Michelle Walker, PhD
DNDP Medical Officer Review	October 22, 2018	Suhail Kasim, MD
DNDP Pharmacology/Toxicology Review	July 10, 2018	Donald C. Thompson, PharmD, PhD
OPQ CMC Review	September 27, 2018	Muthukumar Ramaswamy, PhD

OPQ CMC = Office of Pharmaceutical Quality: Chemistry, Manufacturing and Controls
DMEPA = Division of Medication Error Prevention and Analysis
DNDP = Division of Nonprescription Drug Product

In the United States, Asthma affects an estimated 20 million adults and 6 million children.[2] Asthma is a complex pulmonary disorder characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying airway inflammation.[3] The clinical manifestations of asthma are varying and recurring episodes of cough, wheeze, shortness of breath, and chest tightness. The proposed Drug Facts label (DFL) for epinephrine HFA proposes an indication for "mild symptoms of intermittent asthma" and contains the warning "Do not use unless a doctor said you have asthma." This indication and warning are consistent with the previously marketed epinephrine chlorofluorocarbon (epinephrine CFC) product. This indication and warning are also consistent with the requirements for the labeling of epinephrine when used as a bronchodilator active ingredient in the final monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (21 CFR 341). Mild intermittent asthma is defined by the occurrence of symptoms, use of rescue medication for symptom control, and nighttime awakenings on two or fewer days per week, no interference of normal activities by asthma symptoms, normal baseline lung function, and asthma exacerbations occurring one or fewer times per year.[4] Because of the complexities in the diagnosis and management of asthma, patients with asthma should be under the care of a health care provider for management of asthma, regardless of severity.

Epinephrine is a nonselective (alpha and $beta_2$) adrenergic receptor agonist effective as a short-acting bronchodilator and has been marketed in the United States for the treatment of asthma since the early 1900s. An epinephrine metered dose inhaler (MDI) utilizing a chlorofluorocarbon (CFC) propellant was approved for OTC use for the treatment of symptoms of asthma under NDA 016126 in 1967 (Primatene® Mist). Primatene® Mist was withdrawn from distribution in 2011 in compliance with the Montreal Protocol on Substances that Deplete the Ozone Layer that banned CFC use around the world to protect the environment.

Armstrong's clinical development program included the following:

- First cycle (Original Submission)
  - 3 single dose pharmacokinetic trials in healthy volunteers
  - 2 single dose, dose ranging trials in adults with asthma
  - 12 week Phase 3 safety and efficacy trial in adults and adolescents with an additional 12 week safety extension
  - 4 week safety and efficacy trial in children 4 to 11 years of age

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[2] 2016 National Health Interview Survey (NHIS) Data, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/asthma/most_recent_data.htm; accessed October 21, 2018)

[3] Busse, W, Panel Chair, 2007, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (http://www.nhlbi.nih.gov/guidelines/asthma/index.htm; accessed October 20, 2018)

[4] Busse, W, Panel Chair, 2007, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (http://www.nhlbi.nih.gov/guidelines/asthma/index.htm; accessed October 20, 2018)

  - 3 label comprehension studies
  - 1 human factors study
- Second cycle (first resubmission)
  - 3 label comprehension studies
  - 1 human factors study
- Third cycle (second resubmission)
  - 1 human factors study

Relevant Regulatory History

Please refer to the detailed summary of the regulatory history for epinephrine HFA in the Clinical Review by Suhail Kasim, MD dated October 22, 2018. The relevant regulatory history of epinephrine inhalation aerosol is summarized in Table 2 below.

Table 2 Relevant regulatory history for NDA 205920

November 8, 1967	Original approval of epinephrine inhalation aerosol metered dose inhaler using CFC as propellant (Primatene® Mist) under NDA 016126 (Wyeth Consumer Healthcare)
July 8, 2008	Armstrong acquired Primatene® Mist from Wyeth. Armstrong was the contract manufacturer for Wyeth Consumer Healthcare from 2004 to 2008.
December 31, 2011	Epinephrine inhalation aerosol withdrawn from distribution due to the phase out of the CFC outlined in the Montreal Protocol on Substances that Deplete the Ozone Layer.
October 26, 2009	IND 074286 opened with reformulated epinephrine inhalation aerosol using HFA-134a as propellant
April 8, 2013	NDA submission under NDA 205496 for epinephrine HFA inhalation aerosol (received Refused to File)
July 20, 2013	NDA submission (first review cycle)
February 25, 2014	Joint meeting of the Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee to discuss epinephrine HFA for OTC use
May 22, 2014	Complete Response action due to product quality, nonclinical, and clinical deficiencies
June 28, 2016	NDA resubmission (second review cycle)
December 23, 2016	Complete Response action because the human factors (G3) study failed to demonstrate that the user interface supports safe and effective use of the product by intended users for the proposed uses in the OTC setting
February 5, 2017	Armstrong submitted letter requesting reconsideration of the determinations made in the Complete Response letter dated December 23, 2017.

March 23, 2017	Type A Meeting was held to discuss issues raised in the Complete Response letter dated December 23, 2017 (teleconference)
June 27, 2017	Formal Dispute Resolution Request submitted
September 2, 2017	Formal Dispute Resolution Request denied
November 8, 2017	Armstrong submitted an HF validation (G4) study protocol for review
March 2, 2018	FDA Advice Letter provided feedback for human factors (G4) study protocol design
May 7, 2018	NDA resubmission (third review cycle)

The following recommendations were included in the complete response letter dated December 23, 2016:

1) Further changes to the labeling regarding the mouthpiece instructions, including:
   a) Making the embossed instructions on the mouthpiece more legible, such as by increased contrast between the font and the background.
   b) Aligning the instructional language on the actuator to the revised DFL and consumer information insert.
   c) Adding pictograms, for key steps, to the mouthpiece. This could provide an additional prompt to consumers about correct use when they are having an asthma attack.

2) Consider other approaches to optimizing consumer understanding and use of the device.

3) Re-evaluate the primary task failures and difficulties and their associated root causes, update your risk analysis accordingly, and implement additional risk mitigation strategies as needed. Conduct another human factors (HF) validation study after you implement all changes.

4) Consider designing the HF protocol to include retesting subjects several weeks after the initial test session to simulate intermittent use.

3. Product Quality

The submitted bench data was reviewed by Muthukumar Ramaswamy, PhD from the Office of Pharmaceutical Quality, Controls, Manufacturing, and Chemistry (CMC). Dr. Ramaswamy's recommendation for this NDA resubmission is approval. Based on his

assessment of the bench data, he also recommends that a cleaning frequency of "wash every day if used" and repriming frequency of "reprime before each use" be used for label instructions. Please see the CMC Review by Dr. Ramaswamy dated September 27, 2018 for the full details of his assessment of the bench data. The main points and conclusions in Dr. Ramaswamy's review are summarized below.

During the first review cycle of the NDA submitted on April 25, 2014, CMC recommended a complete response, because the drug substance manufacturing facility (b) (4) was noncompliant for cGMP. Please refer to the Division Director Review by Dr. Theresa Michele dated May 22, 2014 for a summary of the CMC issues addressed during the first review cycle of the NDA.

During the second review cycle of the NDA submitted on June 28, 2016, CMC recommended approval. Please refer to the Division Director Review by Dr. Theresa Michele dated December 23, 2014 and CDTL Review by Francis Becker, MD dated December 9, 2018 for a summary of the CMC issues addressed during the second review cycle of the NDA.

Information reviewed in the previous review cycles for the device and dose indicator showed reliable performance over the lifespan of the product. The epinephrine HFA metered dose inhaler is a standard press-and-breath metered dose inhaler with a top mounted dose actuation indicator and contains 160 metered spray releasing 125 mcg of epinephrine per actuation. The proposed dose is one or two inhalations with instructions to wait at least four hours between doses, with a maximum daily dose of eight inhalations.

Armstrong submitted a risk assessment of deviations in inhaler use instructions. Dr. Ramaswamy evaluated the acceptability of label revisions based on additional bench studies and the risk assessment. Dr. Ramaswamy's review evaluated the use errors associated with the following events:

- Initial prime
  - No initial prime
  - Deviated initial prime from Instructions for Use (IFU)
- Routine use
  - No shaking
  - Pressing off-center during actuation
- Washing
  - No washing for the entire life of the inhaler
  - Spray if wet after washing

  - Not shaking off water after washing
- Reprime
  - No repriming for the entire life of the inhaler

Dr. Ramaswamy states in his review:

> *This CMC reviewer agrees with this approach to justifying potential deviations to labeling instructions for certain low frequency occurrence. The applicant need not have to revise the label revisions to permit deviations as the normal operating procedure with respect to repriming and cleaning frequency.*

Cleaning Frequency Evaluation

The Applicant performed several cleaning studies to determine the acceptable wash frequency. The original NDA submission and the first NDA resubmission contained data supporting the proposed instructions for the cleaning procedure (wash time, wash directions) and the cleaning frequency (b) (4) These results were discussed in the previous two CMC reviews.

The Applicant conducted an additional 20 day simulated use study in which inhalers were used without cleaning. Dr. Ramaswamy concluded that the net effect of not cleaning the actuator would likely be a higher than expected dose due to carryover of the drug from the actuator. However, he noted that the results of the study did not indicate clogging of the actuator, because the delivered dose content did not gradually decrease over the 20 day use period without cleaning.

Dr. Ramaswamy states in his review:

> *During delivery of epinephrine aerosol to the patient, the API (epinephrine) deposits on the valve stem and actuator. The applicant has quantified the amount of API deposited on valve and actuator as ~(b) (4) mg (which ~(b) (4) of the expected (b) (4) mg drug content expected to be on the actuator and valve stem) during the lifetime use of E004 inhaler (b) (4) sprays). The applicant also provided pictures of orifice of inhalers used in the study to indicate they did not clog.*
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> *The applicant also compared the orifice diameter of E004 actuator (b) (4) mm) to other albuterol sulfate aerosol inhalers (b) (4) mm, drug load per actuation, and alcohol content to explain why E004 does not clog in comparison to other commercial inhalers. The applicant's explanation seems to be reasonable.*

Results from this study indicated that the use of inhalers beyond 7 days without cleaning resulted in the delivery of inconsistent dose. Dr. Ramaswamy states in his review:

> *Beyond 7 days of use dose inconsistency is indicated by larger standard deviation for the data set. For example, mean and standard deviation corresponding to 7 to 20 days of use without cleaning (resubmission study) ranged from 103.3 ± 9.2 % to 118.9 ± 19.5%. Compare this result with the use of inhaler for 1 to 7 days without cleaning (101.4 ± 7.1% to 108.4 ± 8.1% LC).*
>
> *Original cleaning study data supported 3 days of use without cleaning. 7 day wash frequency could be considered as best case. The originally proposed labeling instruction "Wash every day if used" is very conservative and should be used for labeling the product.*
>
> *Cleaning study data is useful to justify that potential deviations* (b) (4) *(7 days of use without cleaning the mouthpiece) will not result in patient receiving under dose.*
>
> *Note that the cleaning verification study report does not contain information on aerodynamic particle size distribution data (APSD, respirable dose, % respirable fraction) and spray pattern for the dose dispensed from dirty inhalers. Without these data, I cannot accept the conclusion on the quality of the dose dispensed from a clean actuator is equivalent to the dirty actuator.*

CDTL Comment:

In the original NDA and first resubmission, the instructions to wash the inhaler after every day of use was determined to be acceptable based on the data submitted by the Applicant. (b) (4) *The new cleaning study indicates that there is increased variability in the dose dispensed after seven days of not washing the inhaler. However, the results of the new cleaning study cannot invalidate the original cleaning study data which supported up to three days of use without cleaning and the Applicant's original proposal to wash the inhaler after every day of use. For these reasons, the review team agreed that the labeling include this conservative recommendation of washing the inhaler after every day of use. Also, this conservative approach to the cleaning recommendation avoids the consumer having to keep track of the number of days in between uses.*

Priming Evaluation

The proposed product is an aerosol suspension that can settle easily within the immediate container. Dr. Ramaswamy concluded that the original bench studies and additional data submitted in the resubmission confirm that shaking during priming and repriming are critical steps in using the inhaler correctly. Not shaking the inhaler before first use (priming) or during routine use (repriming) will result in either underdose or supratherapeutic dose. This was supported by the Applicant's study (E004 User Error Risk Report C) evaluating the emitted dose of the inhaler when it is not shaken prior to each dose during the container life (160 sprays). The applicant concluded that the risk of receiving an underdose (less than (b) (4)% LC) from the inhaler is as much as 29% (108 of 368 data points) and the risk of receiving a supratherapeutic dose (greater than (b) (4)% LC) is 9%. Dr. Ramaswamy concluded that shaking the inhaler each time prior to before use is a critical step, and failure to perform this task will result in receiving a low dose or supratherapeutic dose.

The Applicant also provided additional data from bench studies that evaluated the impact of deviations to initial priming on dose content uniformity (E004 User Error Risk Report C and Supplemental Report for Risk Evaluation due to User Errors of "No Initial Priming" or "Deviated Initial Priming"). The Applicant recommends a priming procedure prior to first use in which the inhaler is shaken then sprayed into the air four times prior to first use. The Applicant provided data indicating that 26 out of 28 dose content uniformity (DCU) data points for the first two sprays were less than (b) (4)% of the labeled content (LC). Therefore, when the inhaler is not primed, the probability for the first dose to be an underdose is 86.7%. There were 2 out of 28 data points that were between (b) (4) % LC and considered to be an overdose. None of the data points for the third and fourth sprays were out of the range of (b) (4) %.

The Applicant also provided data on the dose content dispensed from the inhaler after different scenarios of priming. Dr. Ramaswamy found that the mean dose content (average of the first and second spray after priming) was unacceptable after no initial prime and after priming with only one shake and spray. After 1 shake and spray, the mean dose content was 84 ± 22% (range (b) (4)%). The frequency of underdosing was 86.7% and the frequency of overdosing was 6.7%. The other deviations in priming (2 shakes and 2 sprays, 3 shakes and 3 sprays, 1 shake and 4 to 5 sprays in 2 to 15 minutes, and 1 shake and 4 sprays in 30 minutes) resulted in acceptable dose content. Dr. Ramaswamy concluded that "it appears that the wasting only one spray (the first spray), would result in a situation where sub optimal dose is presented for asthmatic relief." However, if an underdose occurs, the label instructs the user to take another dose, that should be within the acceptable range.

CDTL Comment:
The proposed labeling directs the consumer to take another dose if symptoms persist. The bench data indicate that if the inhaler is not primed, and the consumer receives an underdose and symptoms are not adequately relieved, then the second dose will be in the therapeutic range.

Repriming Evaluation

The epinephrine HFA inhaler [redacted] After a period of non-use, the emitted dose content of the first dose from the inhaler may be lower than expected. Repriming frequency was evaluated through two studies – original one week study and a newly submitted 20 day simulated use study. Dr. Ramaswamy evaluated the data from the original study (Summary Report of Product Characterization Studies for Epinephrine HFA MDI) and concluded that a repriming frequency of 24 hours is appropriate based on statistical analysis indicating that after 24 hours of rest time, the probability for the first spray dispensed from the inhaler to be an underdose (< [redacted]%) is 3%.

Dr. Ramaswamy analyzed the data from the 20 day simulated use repriming study and concluded that after 2 days of non-use, underdosing is likely to occur with the first spray. However, results for the first 2 sprays (averaged) indicated that inhalers used in the study dispensed acceptable dose without reprime for up to 14 days.

Regarding the need for [redacted] Dr. Ramaswamy made the following assessment:

> *The applicant is using two spray data to determine the repriming frequency (risk based approach) to justify the need for* [redacted] *The original label instructions required to waste one spray to avoid unacceptable dose.* [redacted]
>
> *This CMC reviewer does not agree with these proposed revisions. Revisions discount previous study results without appropriate justification.*

Dr. Ramaswamy concluded that the original labeling instructions to reprime the inhaler before each use is a conservative labeling recommendation [redacted]

Manufacture

Dr. Ramaswamy reviewed the updated information for the packaging operation and several changes to the manufacturing process. He concluded that the Applicant provided adequate information of the Primatene Mist packaging configuration. He also noted that the Applicant verified visually adhesion stability and legibility of the label through simulated use studies (washing and temperature challenge) and during shipping/transport. Figure 1 below, from Dr. Ramaswamy's review, shows a representation of the packaged unit assembly.

(b) (4)

Active Pharmaceutical Ingredient Manufacturing Facility

At the time of this writing, internal discussions regarding the active ingredient manufacturing facility were ongoing. Armstrong reports that it has acquired sufficient supply of epinephrine API manufactured under GMP by (b) (4) prior to December 2017 to manufacture (b) (4) epinephrine HFA inhalers (b) (4) Armstrong has also agreed that it will (b) (4). The review of the manufacturing facility by the Office of Process and Facilities in the Office of Pharmaceutical Quality is pending.

4. Nonclinical Pharmacology/Toxicology

Donald C. Thompson, PhD was the Pharmacology/Toxicology reviewer for this application. Please refer to Dr. Thompson's review dated July 10, 2018. Dr. Thompson recommends approval of this application from a nonclinical perspective. No nonclinical data were included in the submission. No novel excipients are included in the drug product formulation. Dr. Thompson reviewed the safety of

the thymol excipient for inhalation use during the previous review cycle (see the Pharmacology/Toxicology Review by Dr. D.C. Thompson on November 16, 2016). He concluded that the safety of the thymol excipient for inhalation use was adequately addressed and recommended approval of the NDA. Please refer to the Division Director Reviews by Dr. Theresa Michele dated May 22, 2014 and December 23, 2016 for a summary of the nonclinical pharmacology/toxicology data and assessment for this NDA.

5. Clinical Pharmacology

No clinical pharmacology data were submitted in the May 7, 2018 class 2 NDA resubmission. Please refer to the Division Director Review by Dr. Theresa Michele dated May 22, 2014 for a summary of clinical pharmacology data and evaluation submitted during the first review cycle, and there were no outstanding clinical pharmacology issues identified at that time.

6. Clinical Microbiology

No clinical microbiology data were submitted in the May 7, 2018 class 2 NDA resubmission. Please refer to the Division Director Review by Dr. Theresa Michele dated May 22, 2014 for a summary of clinical microbiology data and evaluation submitted during the first review cycle, and there were no outstanding clinical microbiology issues identified at that time.

7. Clinical/Statistical- Efficacy

No clinical efficacy data were submitted in the May 7, 2018 class 2 NDA resubmission. The results of the efficacy studies were thoroughly reviewed during the first review cycle. For a detailed review and summary of the conducted efficacy trials and the efficacy data, see the Clinical Review by Jennifer Pippins, MD, MPH; Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), dated April 14, 2014. Regarding efficacy, Dr. Pippin concluded that “the clinical program provides evidence of the proposed product’s efficacy as a bronchodilator.” A summary of the efficacy data is also included in the Division Director Review by Theresa Michele, MD dated May 22, 2014.

8. Safety

There were no new clinical trial data submitted for the assessment of safety in this resubmission. During the first cycle review, safety data from the clinical trials were reviewed in the Clinical Review by Ryan Raffaelli, MD dated April 15, 2014. Dr. Raffaelli also

reviewed marketing experience from 1997 to 2012 for Primatene Mist from the pharmacovigilance database, FAERS, data from American Association of Poison Control Centers, and published literature. Please also refer to the Division Director Memo by Theresa Michele, MD dated May 22, 2014 for a summary of the integrated safety review from the first review cycle.

Please refer to the Division Director Memo by Theresa Michele, MD dated December 23, 2014 and the CDTL Review by Francis Becker, MD dated December 9, 2014 for a summary of the integrated safety review from the second review cycle.

Consumer Studies

Please refer to the Division Director Review by Theresa Michele, MD dated December 23, 2016 for a summary of consumer summaries that were reviewed during the first and second cycle reviews. In the first cycle, Armstrong conducted three label comprehension studies and one human factors study. In the second cycle, Armstrong conducted three label comprehension studies and one human factors study. In the third cycle, Armstrong conducted an additional human factors study.

The proposed indication for epinephrine HFA is "for temporary relief of mild symptoms of intermittent asthma." Epinephrine HFA is intended for the relief of mild symptoms by consumers who have been diagnosed with intermittent asthma by a health care provider. Dr. Kasim notes in his review, "because patients with mild disease can experience severe exacerbations with life-threatening consequences, the epinephrine HFA metered dose inhaler product needs to be reliable given the proposed use as a rescue inhaler in the asthmatic population." The proposed DFL includes a consumer warning to "see a doctor" if symptoms persist or worsen.

As an OTC asthma rescue inhaler, it is important that consumers can correctly decide that the product is appropriate for their situation and follow the label to use the inhaler correctly and understand when to see a doctor. Because of the complexities of asthma and the potential life-threatening consequences, all patients with asthma should be under the care of a health care provider. Epinephrine HFA is not intended as an alternative to the care of a health care provider for the management of asthma or to replace any component of a prescribed regimen of therapy.

There are significant differences in the product characteristics between the epinephrine HFA and the previously marketed epinephrine CFC MDI which are summarized in Table 3 below. In his Clinical Review, Dr. Kasim noted:

> *Considering the differences between the CFC and HFA epinephrine products, and that consumers who previously used the epinephrine CFC product may be familiar with and likely use the epinephrine HFA product, diligent adherence to the recommended epinephrine HFA labeled instructions is required for safe and effective use.*

Table 3 Product characteristics of epinephrine HFA and epinephrine CFC

	epinephrine chlorofluorocarbon (CFC) MDI (previously marketed CFC product known as Primatene® Mist)	**epinephrine hydrofluoroalkane (HFA) MDI** (proposed)
Propellant	CFC -withdrawn December 2011	HFA
Drug container	Glass reservoir	Aluminum canister
Dose indicator	Semi-transparent reservoir allowing patients to visually determine when the drug solution was running out	Attached dose counter
Formulation	Solution	Suspension
Use and care instructions	Clean mouthpiece after each use	(b) (4)
Population	Ages 4 years and above	Proposed 12 years and above
Dosing regimen	1 to 2 inhalations every 3 hours; (b) (4)	1 to 2 inhalations every 4 hours; maximum 8 inhalations per day
DRUG FACTS LABEL		
Strength	0.22 mg per inhalation	0.125 mg per inhalation
Uses	For temporary relief of occasional symptoms of mild asthma: wheezing, tightness of chest, shortness of breath	For temporary relief of mild symptoms of intermittent asthma: wheezing, tightness of chest, shortness of breath
Warnings	**Asthma alert** Because asthma can be life threatening, see a doctor if you: • are not better in 20 minutes • get worse • need 12 inhalations in any day • use more than 9 inhalations a day for more than 3 days a week • have more than 2 asthma attacks in a week	**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

Directions	Do not exceed dosage Supervise children using this product Adults and children 4 years and over: • start with one inhalation, then wait at least 1 minute. If not relieved, use once more. Do not use again for at least 3 hours. Children under 4 years of age: ask a doctor	For adults and children 12 years of age and over children under 12 years of age: do not use; it is not known if the drug works or is safe in children under 12. **Before First Use**, activate new inhaler by shaking then spraying into air 4 separate times. **Each time you dose**, Shake then spray into the air one time [redacted] (b) (4) Wait 1 minute. If symptoms not relieved, take a second inhalation by repeating [redacted] (b) (4) . **After use** Wait at least 4 hours between doses Do not use more than 8 inhalations in 24 hours Wash inhaler after each day of use. Run water through mouthpiece for 30 seconds
MDI - metered dose inhaler		

Source: Clinical Review by Suhail Kasim, MD, Table 1, page 12

Human Factor Validation (G4) Study

For this resubmission, Grace Jones, PharmD, BCPS from the Division of Medical Error Prevention and Analysis (DMEPA) concluded "that the HF validation (G4) study results demonstrated that the intended user population can use the proposed product safely and effectively. The DMEPA review team also concluded that proposed labeling may be improved editorially for consistency across all labels and labeling pieces and provided labeling recommendations for the Applicant to implement prior to approval.

Dr. Grace Jones evaluated the human factors validation study report results, the proposed IFU, actuator label, container label, and carton labeling for Primatene Mist for areas of vulnerability that could lead to medication errors. See the Human Factors Study Report and Label, Labeling Review by Grace P. Jones, PharmD, BCPS dated October 19, 2018 for the full details of the review. The main points and conclusions in Dr. Jones' review are summarized below.

Dr. Grace Jones noted that Armstrong addressed Agency recommendations for the HF validation study (G4) protocol and provided the HF study data as requested. The previously reviewed HF validation study (G3) failed to demonstrate that the user interface supports safe and effective use of the proposed product by intended users for OTC use. Armstrong stated that it mitigated the failures seen in the G3 study with the following changes:

- Adding an actuator label on the mouthpiece of the inhaler device as advised in the December 23, 2016 CR letter
- Performing additional bench studies
- Revising language and graphics on the proposed labeling (e.g., IFU was revised to a single page)
- (b) (4)

The HF validation (G4) study evaluated if the newly proposed user interface, including the entire product packaging using a placebo-filled inhaler device, supports the safe and effective use by the intended users for the proposed OTC environment. Please see Dr. Grace Jones' review dated October 19, 2018 for the full details about the study design and assessment of study results.

The study was conducted in 45 participants (30 adults and 15 adolescents) with asthma with and without inhaler experience. A total of 40% of the adult participants and 67% of the adolescents were identified as having low literacy.

The following three critical tasks were evaluated in the HF validation (G4) study:

1. Task 1: Initial prime – Labels and labeling instructs users to shake then spray into the air 4 times.
2. Task 2: Routine use (dosing) – Labels and labeling instructs users to shake the inhaler before taking a dose.
3. Task 3: Washing procedure – Label and labeling instructs users to rinse water through both ends of the mouthpiece for at least 30 seconds.

For Task 1 (initial prime), there were 3 use errors. One of the participants (adult with asthma, inhaler experienced) shook and sprayed the inhaler only one time and stated that she saw spray come out of the nozzle and this is how she confirms activation of her current inhaler. One participant (healthy adult, inhaler naïve, low literacy) performed 4 shakes and 2 sprays. One participant (adolescent with asthma, inhaler experienced, low literacy) shook once and sprayed 4 times in rapid succession and stated that this is how she usually does it. According to the evaluation of the bench data by Dr. Ramaswamy (see Section 3) the mean dose content (average of the first and second spray after priming) may be lower than expected without the initial priming step or after priming with only one shake and spray. However, the mean dose content for the third and fourth sprays (average) were found to be acceptable.

Therefore, if a consumer fails to prime the inhaler correctly and receives a lower than expected dose, the label directions instruct consumers to take another dose if symptoms are not relieved, and the bench data indicate that the second dose is likely to provide an appropriate dose.

For Task 2 (routine use), there were 2 use errors that Dr. Jones concluded were due to study artifacts. The two participants did not shake the inhaler prior to dosing because they had just shaken the inhaler in the previous step.

For Task 3 (washing procedure), there was 1 use error. One participant (adult with asthma, inhaler experienced) did not remove the cannister before washing the actuator and ran water through the mouth piece end. The participant stated that this is her usual procedure for washing her inhaler. Taking into consideration Dr. Ramaswamy's review of the bench data and that the actuator orifice is unlikely to clog, washing is not considered a critical task. Therefore, Dr. Jones concluded that there is no safety impact associated with this error.

The G4 study also included a knowledge probe question about repriming the inhaler after two weeks of non-use. There were two use errors with this knowledge probe question. One participant (healthy adult, inhaler naïve, low literacy) stated to wash the inhaler. Another participant (healthy adolescent, inhaler naïve, low literacy) stated to shake but not spray the inhaler. Based on the evaluation of the bench data by Dr. Ramaswamy (see Section 3), the two spray data showed adequate dose content uniformity after two weeks of non-use. However, the one spray data demonstrated that after 2 days, the first dose may be an underdose. Therefore, the review team agreed that the more conservative approach of recommending shake and spray before each dose is appropriate.

The DMEPA team agreed with the review team's assessment and conclusion to revise the instructions. Regarding the need for another HF validation study, DMEPA stated:

> *We determined these changes in the instructions do not require another HF validation study because the critical tasks were adequately assessed in the submitted HF validation (G4) study (i.e., initial prime of shake then spray 4 separate times, shake before each inhalation, and washing the inhaler). In addition, we do not expect the change in frequency of inhaler washing (i.e. from* (b) (4) *to "after each day of use") to impact users ability to perform this task successfully. Furthermore, while we note* (b) (4) *is not critical to the safe and effective use of the product, the conservative labeling recommendation to re-prime before each inhalation increases the likelihood that a user re-primes the inhaler more often. This would improve user performance and minimize the risk of dispensing a variable or inconsistent dose.*

Number of Available doses per Epinephrine HFA MDI

During the joint meeting of the Nonprescription Drugs and Pulmonary-Allergy Drugs Advisory Committees,[5] committee members

[5] The details and links to the advisory committee briefing material including the meeting minutes and transcript may be accessed at the archived webpage http://wayback.archive-

raised a potential safety concern regarding the high number of actuations per inhaler that may encourage chronic use and delay health care provider visits. The availability of the epinephrine HFA product for nonprescription use should not be viewed by the consumer as an alternative to being under the care of a health care provider for managing their asthma. Please refer to Clinical Review by Ryan Raffaelli, MD dated April 14, 2014 (Section 9.3) for a summary of these deliberations by the advisory committees.

During internal meetings for the NDA 205920 resubmission, the review team considered the concerns raised during the advisory committee meeting and assessed the safety of the proposed number of actuations per inhaler (160 sprays). To determine a safe and reasonable number of sprays per inhaler, the review team considered (b) (4) . Per the proposed DFL, the maximum daily dose is 8 inhalations. Therefore, each inhaler (b) (4) when used as labeled. According to the National Institutes of Health Expert Panel Report 3 Guidelines for the Diagnosis and Management of Asthma,[6] asthma is classified as "intermittent" when symptoms occur on two or fewer days per week. Therefore, a consumer with intermittent asthma might use a rescue inhaler twice a week or 8 days in a month. Based on this assessment, the review team concluded that the proposed 160 sprays per inhaler (b) (4) when used as labeled was acceptable.

Dr. Kasim provided the following rationale for approving the proposed container size of 160 inhalations in his Clinical Review:

> *The expected users of the epinephrine HFA metered dose inhaler are asthma patients diagnosed with mild asthma who are managed with short acting beta agonists and or other asthma control prescription medications, and are occasionally in need of an acute asthma relief medication that can be obtained as a nonprescription product between the next prescription refill or interval healthcare visits. There may also be the situations when the user's regular prescription acute asthma relief medication may not be available because of travel or the prescription medications are not easily accessible to them during the acute episode for symptom control because of their very intermittent symptoms experienced. In these circumstances the nonprescription epinephrine HFA metered dose inhaler is expected to provide relief. It is conceivable that asthma patients in some geographic locations of the United States may not have access to a healthcare provider regularly for adequate asthma management. In these circumstances, it is most helpful to have the nonprescription epinephrine HFA product available for managing their intermittent asthma symptoms until their next visit with a healthcare provider for poor symptomatic control* (b) (4)

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it.org/7993/20170111194827/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/ucm380890.htm under the section February 25, 2014 Meeting of the Nonprescription Drugs Advisory Committee (accessed October 18, 2018).

[6] Busse, W, Panel Chair, 2007, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (http://www.nhlbi.nih.gov/guidelines/asthma/index.htm; accessed October 8, 2018)

> *The proposed inhaler presentation with 160 total sprays expected to provide 80 usable inhalations suitable for 10 days of labeled nonprescription use appears acceptable for clinical use and does not pose any additional risk.*

However, to mitigate the risks of chronic use, delayed or discontinued visits to a health care provider for management of asthma, restrictions in packaging configurations are to be considered. Further, Dr. Kasim stated:

> *The reviewer recommends measures to mitigate the risk of deferred care for poorly controlled asthma with package limitations or preventing co-packaging of the epinephrine HFA inhalers in multipacks for nonprescription use. Communications with Armstrong and to future generic product sponsors is additionally recommended to deter manufacturing larger than the 160 spray fill sizes of the drug packaged in the metered dose inhaler.*

During a teleconference held with Armstrong on October 19, 2018, DNDP communicated to Armstrong that as discussed at the Advisory Committee meeting in 2014 regarding the potential for chronic use and delayed health care visits due to the high number of actuations per inhaler; if Armstrong is interested in marketing other package configurations in the future (e.g., immediate containers containing greater than 160 metered sprays, package sizes containing more than one inhaler), then DNDP expects submission of a prior approval supplement that includes justification of why larger package sizes will not adversely impact the safety of the product.

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application during this review cycle. During the first review cycle, a Joint Meeting of the Nonprescription Drugs and Pulmonary Allergy Drugs Advisory Committees was held on February 25, 2014 to discuss the efficacy, safety and overall benefit-risk profile of the product for the treatment of mild symptoms of intermittent asthma in the OTC setting.[7] For a detailed summary of the advisory committee meeting, see the Clinical Review by Ryan Raffaelli, MD dated April 15, 2014.

[7] The details and links to the advisory committee briefing material including the meeting minutes and transcript may be accessed at the archived webpage http://wayback.archive-it.org/7993/20170111194827/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/ucm380890.htm under the section February 25, 2014 Meeting of the Nonprescription Drugs Advisory Committee (accessed October 18, 2018).

10. Pediatrics

The proposed product triggers the Pediatric Research Equity Act (PREA), because it is a new dosing regimen for epinephrine inhalation aerosol. Please refer to the Clinical Review by Ryan Raffaelli, MD dated December 19, 2016 (Section 1.4) for the recommendations requiring pediatric studies under the Pediatric Research Equity Act (PREA).

DNDP discussed NDA 205920 with the Pediatric Review Committee (PeRC) on November 16, 2016. PeRC agreed that a partial waiver was acceptable, because children under four years do not have the dexterity or coordination of efforts to reliably manipulate the inhaler device, and therefore clinical studies in this age group would be impossible or highly impracticable.

Required PREA studies included the conduct of a deferred multiple dose safety and efficacy trial with three arms in pediatric patients with asthma who are 4 to 11 years of age, comparing a two-inhalation dose of the test product epinephrine inhalation HFA (125 mcg/inhalation), a one-inhalation dose of the test product, and placebo. The trial must include an assessment of epinephrine exposure around T_{max} (b) (4) in the safety and efficacy trial. (b) (4) as discussed in the Clinical Pharmacology review by Jianmeng Chen, MD PhD dated December 9, 2016.

On October 19, 2018, Armstrong submitted a letter to the DNDP with the agreed upon dates of completion for the required pediatric studies:

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

11. Other Relevant Regulatory Issues

No additional relevant regulatory issues were identified during this review cycle.

12. Labeling

Prescribing Information

Prescribing information is not applicable to this OTC product, see Consumer Labeling below.

Consumer Labeling

Proprietary Name

The proprietary name reassessment was conducted by the DMEPA team: Grace P. Jones, PharmD, BCPS, Reviewer; Chi-Ming (Alice) Tu, PharmD; Danielle Harris, PharmD, BCPS. The proposed proprietary name, Primatene Mist, was found conditionally acceptable on August 29, 2018.[8]

During the second cycle review, Armstrong resubmitted the proprietary name (b) (4) for review. (b) (4) Armstrong subsequently proposed the name Primatene Mist, that was found to be acceptable on November 1, 2016.[9]

Consumer Labeling

Michelle Walker, PhD conducted the DNDP labeling review. Please refer to the Labeling Review by Dr. Michelle Walker dated October 15, 2018 for the full details of the review. The outer carton Drug Facts label (DFL), immediate container label, actuator label, and consumer information insert[10] were reviewed. The Primatene Mist website content was also reviewed, because the website address is included in the outer container label. Instructional videos on the correct use of the epinephrine HFA inhaler are also included on the website. Based on the labeling changes made during this review cycle, Armstrong produced new videos to align with the new labeled directions for use. Please see Appendices for the most recent draft carton label (Appendix 1), consumer information insert (Appendix 2), actuator label (Appendix 3), and the Asthma Learning Center page on the product website (Appendix 4) at the time of this writing.

The DMEPA review team also reviewed the labels and labeling and provided recommendations for editorial improvements for consistency across all labels and labeling pieces. Please refer to the Human Factors Study Report and Label, Labeling Review by Grace P. Jones, PharmD, BCPS dated October 19, 2018 for the full details of the review.

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[8] Proprietary Name Review by Grace Jones, PharmD, BCPS dated August 29, 2018.

[9] Proprietary Name Review by Grace Jones, PharmD, BCPS dated November 1, 2016.

[10] The consumer information insert is also referred to as the Information for Use (IFU) in Section 8.

Armstrong modified the consumer instruction for use with simplified steps so that information is now presented only on one side of a page and aligned the instructional language on the actuator to the revised DFL and consumer instructions for use. Also, carton modifications were made such that the consumer instructions for use needs to be removed prior to using the inhaler. Armstrong also modified the labeling on the device actuator and mouthpiece with pictograms incorporating DNDP recommendations based on the concerns that consumers may not have immediate access to the DFL or consumer instruction for use when the inhaler is being used.

Based on the CMC bench data analysis as summarized in Section 3 above, the review team recommended the following two changes:

- Wash after every day of use: Bench data indicated increased variability in dose content after seven days of not washing the inhaler that may potentially lead to supratherapeutic doses. The original cleaning study supported three days of use without cleaning, and the original proposed labeling instruction to wash after every day of use was determined to be acceptable in the previous cycle review. Thus, the review team agreed that the conservative recommendation to wash the inhaler after every day of use is preferred to provide consistent dosing, and because consumers will otherwise have to keep track of how many days they have used the inhaler before washing it.

- Shake then spray into the air before each dose: The suspension can settle and lead to dose variability. Dr. Ramaswamy determined that the recommendation to reprime the inhaler (shake then spray into the air) after two weeks of non-use discounts previous study results without appropriate justification. Repriming before each dose is the conservative approach and will provide the most consistent dose to the consumer. Also, because epinephrine HFA is intended for intermittent use, consumers may not remember how long it has been since they took the last dose.

The review team also reviewed the website text because the website is considered part of labeling. The review team made recommendations for changes to the website text to be consistent with the other labeling. Also, the Primatene Mist website contains instructional videos on the correct use of the product that also needed to incorporate the recommended changes to the labeled directions for use. The website also contained an “Asthma Learning Center” which appears to provide general information about asthma as well as information about asthma triggers such as allergies, smoking, cold air; and all the information in the “Asthma Learning Center” are not applicable to epinephrine HFA. Therefore, the review team recommended edits to the “Asthma Learning Center” to add information about the labeled indication for epinephrine HFA and to add the same Asthma alert that is in the DFL to the top of the webpage to remind consumers to see a doctor for worsening or persistent asthma symptoms. Also, the review team recommended adding a statement to the website to point out that although epinephrine HFA contains the same active ingredient as epinephrine CFC, the two inhalers work differently.

On October 2, 2018, a teleconference was held with Armstrong to discuss the recommended changes to the directions and labeling. Armstrong agreed with the changes including changes to the product website information and instructional videos on the website and submitted revised labeling that incorporated the recommended changes on October 9, 2018.

The labeling recommendations from DMEPA can be found in Sections 4.1 and Appendix H of Dr. Jones' review dated October 19, 2018.

At the time of this writing, labeling discussions are ongoing and the formatting of the DFL and the immediate container label have yet to be finalized. Armstrong slightly modified the Directions section to comply with the bullet formatting requirement in 21CFR 201.66(d)(4), and to ensure all sections have the same type and style of bullets. Specifically, the subheading Each Time you Dose that listed the steps using a sequential numbering format was modified to the bulleted 5 point solid square format. DMEPA indicated that they would support the numbered format if an exception could be made and if the change was feasible because the numbered format prompts the user to the sequence of the steps and to follow the steps to use the drug properly.

CDTL Comment
Although I agree with DMEPA's rationale for recommending sequential numbering in the Directions section, I find that the use of the bulleted format is acceptable because it complies with 21 CFR 201.66(d)(4) and the numbering is used in other components of the labeling including the consumer information insert, actuator label, and website indicating the correct sequence of steps needed to use the inhaler correctly.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Routine postmarketing surveillance is appropriate.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Please see Section 10 above for a discussion of the PMR for pediatric studies under PREA for this application.

14. Recommended Comments to the Applicant

I recommend approval of the OTC marketing of epinephrine inhalation aerosol with hydrofluoroalkane propellant in a metered dose inhaler (epinephrine HFA), at a dose of 125 mcg/actuation for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. The Applicant has adequately addressed the Complete Response issues in the FDA Complete Response letter dated December 23, 2016. My recommendation for approval is contingent upon agreement with the Applicant on appropriate product labeling.

Recommended Comment to Applicant:

If you are interested in marketing other package configurations in the future (e.g., immediate containers containing greater than 160 metered sprays, package sizes containing more than one inhaler), we expect submission of a prior approval supplement that includes justification of why larger package sizes will not adversely impact the safety of the product. Consider requesting a meeting with us prior to submission of such a supplement, to discuss safety implications and your proposed justification to support a larger package configuration.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

JENNY L KELTY
10/24/2018