CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

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.*
>
> *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] (b) (4) 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 (< (b) (4) %) 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] (b) (4) 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] (b) (4) *The original label instructions required to waste one spray to avoid unacceptable dose.* [redacted] (b) (4)
>
> *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] (b) (4)

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

Cross-Discipline Team Leader Review

Date	December 9, 2016
From	Francis E. Becker, M.D., F.A.C.P.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	205920, SD-39
Applicant	Armstrong Pharmaceuticals, Inc.
Date of Submission	28 June 2016
PDUFA Goal Date	28 December 2016
Proprietary Name / Non-Proprietary Name	Primatene Mist/Epinephrine Inhalation Aerosol (epinephrine HFA)
Dosage form(s) / Strength(s)	125 mcg/inhalation; 1-2 inhalations every 4 hours as needed; not to exceed 8 inhalations in 24 hours
Applicant Proposed Indication(s)/Population(s)	Temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Not applicable.

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

I recommend a Complete Response action be taken for this application. It is likely that a significant percentage of users will incorrectly use the device and therefore receive an inadequate dose. It is unclear whether consumers who select to use this product will be appropriate for the proposed indication, that is "mild symptoms of intermittent asthma" or whether consumers with more severe or persistent asthma will use this product, and it is unclear if consumers who use the product and do not experience adequate relief of symptoms will appropriately follow the "see a doctor" warnings, because these scenarios have not been adequately tested. I recommend that the Sponsor conduct an Actual Use Trial (AUT) which will help provide answers to these uncertainties associated with potential over-the-counter (OTC) use of this product.

Asthma is a chronic inflammatory disease characterized by varying and recurring symptoms of shortness of breath, chest tightness, wheezing and cough. In the United States, asthma affects more than 22 million persons. Medications for asthma treatment are categorized into two classes: quick relief medications to treat acute symptoms and exacerbations and long-term medications to achieve and maintain

control of persistent asthma. Inhaled short-acting $beta_2$ agonists (SABAs) are used as quick relief of bronchospasm and are the mainstay of therapy for acute treatment. Inhaled SABAs are currently available by prescription only. Thus, if approved, the proposed product would be the only SABA available without a prescription.

Patients with mild, intermittent asthma, which is generally defined as symptoms 2 or fewer days per week, nighttime awakenings 2 or fewer times per month, use a short-acting beta agonist for symptom control 2 or fewer days per week, have no interference of normal activities by asthma symptoms, have normal baseline function, and experience one or fewer exacerbations per year, are targeted for this indication. Patients with more frequent or persistent symptoms should be under a physician's care and may receive more extensive medical treatment.

The safety and efficacy profile of the proposed product for the proposed indication at the proposed dosage (125 mcg per spray) is acceptable. Clinical efficacy trials were conducted by the Sponsor and submitted during the first review cycle provided clear evidence of the proposed product's efficacy as a bronchodilator at the intended dose. Known safety concerns associated with epinephrine administration include transient hyperglycemia, hypokalemia, increases in blood pressure or heart rate, or arrhythmias. However, the inhaled drug is minimally absorbed, having its effect primarily on beta receptors in the respiratory tract within 1-5 minutes. In addition, several pharmacodynamic safety studies indicated that the resultant drug levels at doses nearly 13-fold higher than proposed (125 mcg versus 1600 mcg in one trial) were not likely associated with significant safety issues.

However, the studies submitted in this submission (three label comprehension studies [LCS] and one human factors [HF] study) raised concerns about whether or not consumers could use the product correctly. Approximately 30% of participants in the Human Factors Study failed at least one of the three primary tasks of the study: failure to adequately complete initial priming, failure to adequately clean the device to prevent clogging, or failure to adequately re-prime the inhaler for continued routine use. This is a significant clinical concern, because, if these tasks are not correctly performed, users of this product may not correctly administer the product and therefore may under-dose or receive a supra-therapeutic dose. Clinically, because of the wide safety margin, a supra-therapeutic dose is unlikely to be problematic. However, under-dosing may result in lack of efficacy. Furthermore, results suggest that subjects with low literacy level and those with prior inhaler experience (former users of Primatene Mist epinephrine-CFC) did not perform as well in these tasks. It is possible that former users of Primatene Mist (epinephrine CFC) or those in low income areas who do not have access to a physician and who may be more likely to be in the low literacy category are more likely to puurchase this product OTC if it is approved.

The risk can be mitigated to some extent. It is possible that some users who improperly use the device initially will receive the correct dose after repeated use, and, as noted above, if a user receives 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. Furthermore, proposed labeling advises users to see a doctor if they are 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.

However, the labeling warnings are derived from OTC monograph language and have not been tested in consumer studies. Therefore,

comprehension of these warnings is unknown. It is also unclear if users will recognize if they are getting worse or not better and see a doctor as recommended. Furthermore, it is unclear if users will accurately select to use the product, that is, it is unknown if users with persistent or more severe asthma will attempt to use this product, not be under the care of the physician, and not be able to recognize that there symptoms are not appropriate for OTC treatment. It is also possible that a user should be advised to "go to the emergency room" or "seek immediate medical attention" as opposed to "see a doctor," as seeing a doctor does not imply urgency and may involve a lengthy process of calling for and scheduling an appointment, especially if the consumer does not already have a physician.

Conversely, an argument can be made that, for users in remote rural errors or those who do not have access to a physician, having this product available may be preferred to having no product available, and it is unclear if the behavior of asthma sufferers in this group as far as seeking medical attention if they do not get better would be any different whether they have the product available for use or not. Perhaps, even if the product does not work because of improper use, users would benefit from having a warning to read advising them to see a doctor, as opposed to not having any product or labeling and having to make a decision about what to do on their own.

It is unlikely that labeling mitigation would eliminate medication errors entirely. Post-marketing errors with prescription HFA products with similar product-user interfaces, have been reported despite their use under a prescriber's supervision. These known use errors with prescription HFAs are similar to those observed in the HF study. Thus, it is anticipated that use errors for the proposed product will be similar to those observed with the prescription products, if approved.

An AUT would be important to address the questions raised, including: whether consumers appropriately select to use the product, whether they can correctly use the product in a real world scenario when they are suffering from an asthma attack, and what will be their subsequent behavior if they fail to improve, that is, will they follow labeling warnings and correctly seek medical attention if needed? The Sponsor was previously advised to conduct an AUT. In the Complete Response (CR) letter of 22 May 2014, FDA stated, "After conducting smaller behavioral (human factor) study(ies) to refine the labeling and potentially the device, conduct a randomized, actual use study with the revised labeling and proposed epinephrine HFA inhalation aerosol to rigorously quantify and evaluate complaints or problems associated with use of the product and characterize sources of user error." The Sponsor chose not to do an AUT, claiming that it would be difficult to field such a study because mild sufferers only have occasional episodes; therefore, most episodes involving Primatene use would probably be beyond the timeline scope of a study. However, I disagree. As Ms. Cohen of Social Science pointed out, an actual use study could not only assess users' problems with the product, but it could also independently assess the severity of asthma symptoms of those who chose to purchase the product, which might be helpful in refining benefit/risk calculation. Furthermore, in an AUT, the Sponsor could advertise for sufferers of mild symptoms of intermittent asthma (in other words, the labeled indication for this product) and then assess whether the sufferers' definition of "mild" and "intermittent" is in fact aligned with the Sponsors's definition of "mild", and "intermittent" by assessing actual patterns of usage and any difficulties with the use of the product.

In conclusion, potential lack of efficacy due to incorrect usage of the product is the main clinical safety concern. A product for whom 30% of intended users may not be able to correctly administer may not be appropriate for OTC use unless there is clear demonstration that this number can be adequately mitigated in a real world scenario.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Asthma is a chronic inflammatory disease characterized by varying and recurring symptoms of shortness of breath, chest tightness, wheezing and cough. • In the United States, asthma affects more than 22 million persons.	The proposed epinephrine-HFA proposes an indication for "mild symptoms of intermittent asthma, which is generally defined as symptoms 2 or fewer days per week, nighttime awakenings 2 or fewer times per month, use a short-acting beta agonist for symptom control 2 or fewer days per week, have no interference of normal activities by asthma symptoms, have normal baseline function, and experience one or fewer exacerbations per year. This is an appropriate indication.
Current Treatment Options	• Medications for asthma treatment are categorized into two classes: quick relief medications to treat acute symptoms and exacerbations and long-term medications to achieve and maintain control of persistent asthma.Inhaled short-acting beta$_2$ agonists (SABAs) are used as quick relief of bronchospasm and are the mainstay of therapy for acute treatment. Inhaled SABAs are currently available by prescription only.	If approved, epinephrine inhalation aerosol would be the only short acting inhaler available over-the counter for the proposed indication.
Benefit	• Clinical efficacy trials were conducted by the Sponsor and reviewed during the first review cycle and provided clear evidence of the proposed product's efficacy as a bronchodilator at the intended dose. The inhaled drug is minimally absorbed, having its effect primarily on beta receptors in the respiratory tract within 1-5 minutes.	Efficacy of the proposed product for the proposed indication has been adequately demonstrated.
Risk	• Safety data was reviewed during the first review cycle. Several pharmacodynamic safety measures indicated that the resultant drug levels at doses nearly 13-fold higher than proposed (125 mcg versus 1600 mcg in one trial) were not likely associated with significant safety issues of concern with this product (transient hyperglycemia, hypokalemia, increases in blood pressure or heart rate, or arrhythmias). No additional safety data was submitted with this completed response. • Approximately 30% of participants in the Human Factors Study failed at least one of the three primary tasks: failure to adequately complete initial priming, failure to adequately clean the device to prevent clogging, or failure to adequately re-prime the inhaler for continued routine use. • In the human factors study, subjects with low literacy level and	There is no product data identifying a cardiovascular or other serious safety adverse event when the product is used as intended at the recommended dosage. Moreover, the safety margin for cardiovascular adverse events is very high. Users of this product may not correctly administer the product and therefore may under-dose (in which case efficacy is less likely to be achieved) or receive a supra-therapeutic dose. It is possible that, if this product is approved, it will be more likely to be used by former users of Primatene Mist (epinephrine CFC) or those in low income areas who do not have access to a physician and who may be more likely to be in the low literacy category.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	those with prior inhaler experience did not perform as well in all tasks.	
Risk Management	• Proposed labeling appropriately 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 a user receives a supratherapeutic dose because they did not use the product correctly, they will receive and efficacious dose and will not be at risk for cardiovascular or other serious adverse events. • It is possible that some users who improperly use the device initially will receive the correct dose after repeated use.	The labeling warnings have not been tested in consumer studies. Therefore, comprehension of these warnings is unknown. It is also unclear if users will recognize if they are getting worse or not better and see a doctor as recommended. It is also possible that a user should be advised to "go to the emergency room" or "seek immediate medical attention" as opposed to "see a doctor," which may involve a process of calling for an appointment. Conversely, an argument can be made that, for users in remote rural errors or those who do not have access to a physician, having this product available may be preferred to having no product available, and it is unclear if the behavior of asthma sufferers in this group as far as seeking medical attention if they do not get better would be different . Perhaps, even if the product does not work because of improper use, users would benefit from having a warning to read advising them to see a doctor. In addition, it is unlikely that labeling mitigation would eliminate medication errors entirely. Post-marketing errors with prescription HFA products with similar product-user interfaces, have been reported despite their use under a prescriber's supervision. These known use use errors with prescription HFAs are similar to those observed in the proposed product HF study. Thus, it is anticipated that use errors for the proposed product will be similar to those observed with the prescription products, if approved.

2. Background

Amphastar Pharmaceuticals, Inc (the Sponsor) is seeking approval for the over-the-counter (OTC) marketing of a hydrofluoroalkane (HFA)-propellant epinephrine inhalation aerosol (125 mcg/inhalation; epinephrine HFA) for adults and children 12 years of age and older. The product, also referred to in studies as E004, is proposed for the temporary relief of mild symptoms of intermittent asthma. This is a similar indication to that approved by FDA in 1967 for a predicate OTC product, Primatene Mist, also an epinephrine aerosol. The proposed dosage is 1 to 2 inhalations (Start with 1 inhalation. Wait at least 1 minute. If not relieved, use once more.). Proposed labeling advises users to wait at least 4 hours between doses, and to not use more than 8 inhalations in 24 hours. The current submission constitutes the Sponsor's resubmission of the application following a Complete Response (CR) action by the Division of Nonprescription Drugs (DNDP).

Epinephrine is a bronchodilator (short-acting $beta_2$-agonist) and has been marketed in the United States for use in the treatment of asthma since the early 1900s. An oral metered dose inhaler (MDI) formulation utilizing a chlorofluorocarbon (CFC) propellant (Primatene Mist) was approved for OTC use for the treatment of symptoms of asthma on 8 November 1967 under NDA 016126 and was originally marketed by Wyeth Consumer Healthcare. Armstrong Pharmaceuticals, Inc. was the contract manufacturer of Primatene Mist for Wyeth from 2004 to 2008. On 8 July 2008, Armstrong acquired Primatene Mist from Wyeth.

MDIs using CFC propellants began to be phased out in 1996 following ratification of the Montreal Protocol on Substances that Deplete the Ozone Layer (US ratification – 1988) which banned CFC use around the world to protect the environment. A proposed rule for phase out of epinephrine CFC MDIs was published in 2007, and a Final Rule (2008) established 31 December 2011 as the end date for use of CFCs in epinephrine MDIs. CFC-based Primatene Mist was phased out of the US market in 2011. Armstrong marketed the product until it was withdrawn from distribution on 31 December 2011.

The Sponsor originally submitted NDA 205920, a 505(b)(2) new drug application for a reformulation of Primatene Mist using hydrofluorolkane (HFA) propellant, on 22 July 2013. Three label comprehension studies (I, II, and III) and one human factors study were included in the NDA. The application was also discussed at a joint meeting of the Nonprescription Drugs Advisory Committee (NDAC) and the Pulmonary Allergy Drugs Advisory Committee (PADAC) on 25 February 2014, where FDA presented concerns about the device performance, given the relatively high number of device malfunctions and dose indicator errors reported in clinical studies.

Following submission of additional analyses of device and dose indicator performance, FDA sent a Complete Response to the Sponsor on 22 May 2014. Along with deficiencies in Good Manufacturing Practices (GMP) and in data supporting the safety of chronic inhalation of thymol, the letter cited the high number of device malfunctions in the clinical trials, including apparent user errors with the dose indicators and also with clogging of the device. The results from the label comprehension studies and human factors study also supported these usability

issues, in that there were limitations in consumer's understanding of critical information such as: not relying on the dose indicator if dropped; the need to prime the indicator before using the first time; the need to clean the product daily after use; and the need to reprime when wet.

In the CR letter, FDA provided the following important points to the Sponsor:

Nonclinical:

The proposed epinephrine HFA inhalation aerosol includes thymol, which is not a qualified excipient for oral inhalation products intended for chronic use. Therefore, the Sponsor was advised to "provide information supporting the safety of chronic inhalation of thymol. If such information is not currently available, conduct a repeat dose inhalation toxicity study of 6 months duration in an appropriate species that shows no adverse findings to support the use of thymol in your product."

Clinical:

The submitted data did not support the proposed OTC use of epinephrine HFA inhalation aerosol for the temporary relief of mild symptoms of intermittent asthma in adults and adolescents 12 years of age and older. The CR letter states, "we note the complexity of the steps required for shaking, priming, actuation, and cleaning in order to ensure adequate product performance," and "raise concerns about consumers' ability to use your epinephrine HFA inhalation aerosol product for the acute treatment of asthma in the OTC setting. This usability issue is concerning 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). To address these deficiencies:

1. Revise the labeling to optimize comprehension and assess the revised label in a label comprehension study. Optimize the labeling to improve comprehension of the following critical information: prime before first use of the product, clean the product on each day of use, reprime the inhaler when wet, do not rely on the dose indicator if dropped, instructions on removing the canister for cleaning and proper reassembly, press on the center of the dose indicator, and orientation of product during use and storage.
2. Conduct a behavioral (human factors) study with the revised label using the actual product (not a dummy product) to assess consumers' ability to use epinephrine HFA inhalation aerosol. Include sufficient numbers of consumers with low literacy in your population assessed against target thresholds; ideally this population should be representative of the proportion of adults in the United States with basic literacy skills based on available national data. Based upon the findings of the behavioral study, further changes to the label or the device may be necessary and additional behavioral (human factor) study(ies) may be necessary.
3. After conducting smaller behavioral (human factor) study(ies) to refine the labeling and potentially the device, conduct a randomized, actual use study with the revised labeling and proposed epinephrine HFA inhalation aerosol to rigorously quantify and evaluate complaints or problems associated with use of the product and characterize sources of user error."

The letter further states that, "Depending on the results of the above iterative evaluations, modification of the product and product labeling may be necessary to minimize potential user error, e.g., revised patient instructions for use, replacement of the current dose indicator with an integrated dose counter, product reformulation and product change to simplify the steps required for adequate product performance, etc. Changes to the product may necessitate additional *in vitro* or clinical data for support."

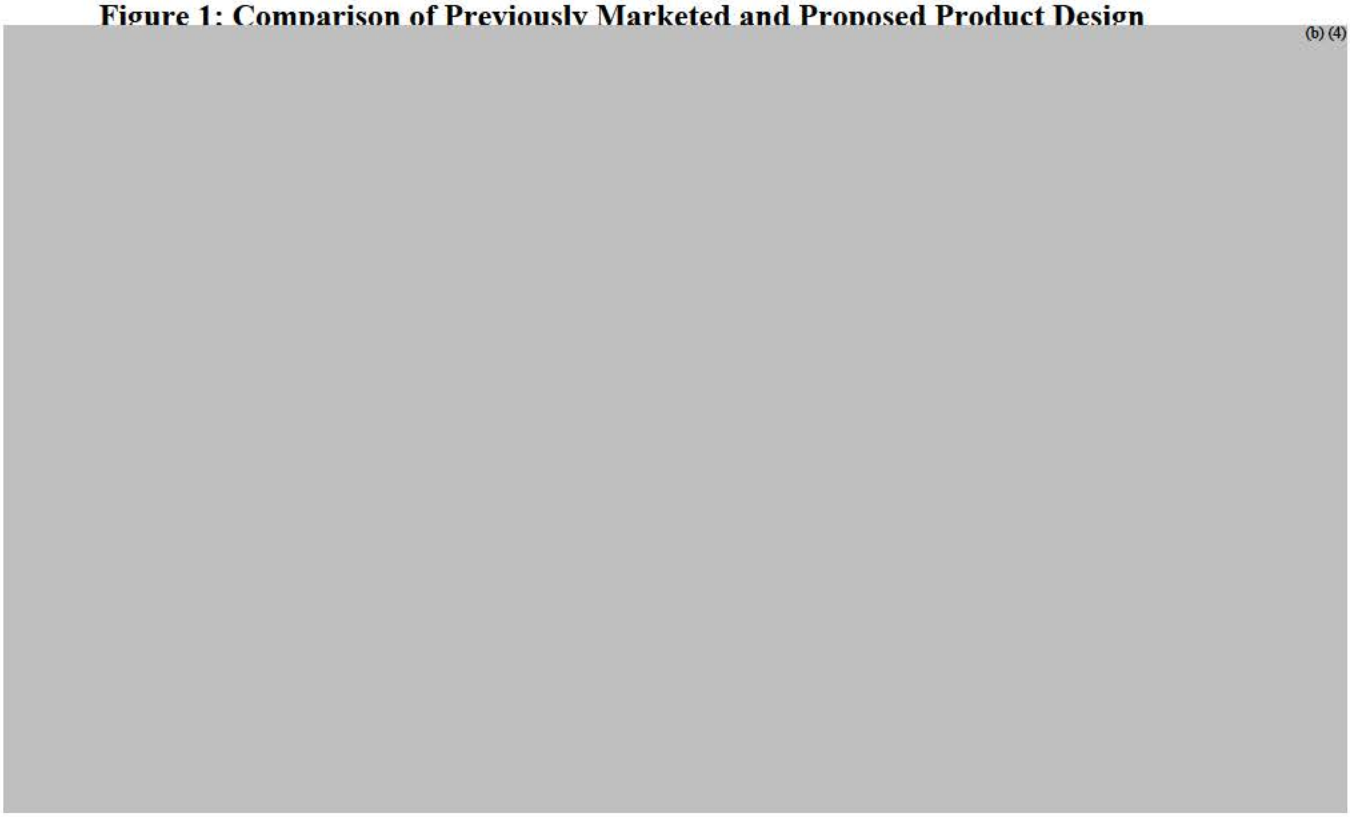
In addition, the CR letter cited pending resolution of GMP deficiencies associated with the drug substance manufacturing facility (b) (4)
Under **Additional Comments**, the CR letter conveyed the CMC recommendation that the sponsor: 1) incorporate acceptance criteria for accuracy into the dose indicator specification; and 2) propose a sampling plan and acceptance quality limit (AQL), for example, (b) (4) % for regular inspection, for dose counter accuracy testing.

In this CDTL Review, I will focus on issues relevant to the Complete Response. The reader is referred to the first cycle reviews for additional information.

3. Product Quality

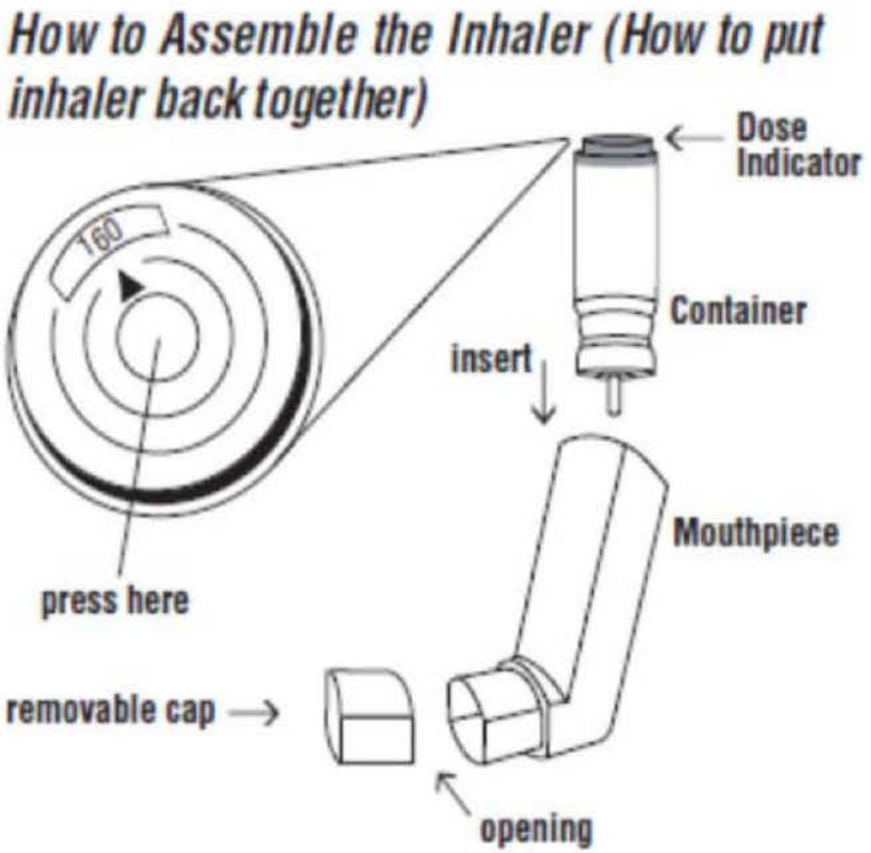
The proposed product, epinephrine inhalation aerosol, is a complete redesign of the original Primatene Mist CFC inhaler (see **Figure 1** below), which was an aerosol solution of epinephrine packaged in a glass (semi-transparent) bottle fitted with a metered dose inhaler (MDI) valve and a mouthpiece. The reformulated product is a suspension in a metal container and contains (b) (4) epinephrine, (b) (4) HFA-134a, 1.000% ethanol, (b) (4) thymol, and (b) (4) polysorbate 80.

Figure 1: Comparison of Previously Marketed and Proposed Product Design



The reformulated product is packaged in a 14mL (b) (4) aluminum canister fitted with a (b) (4) 50µl (b) (4) metering valve, a (b) (4) L shape orange actuator and a (b) (4) dose indicator glued to the bottom of the canister for displaying the number of doses left in the canister, as illustrated in the **Figure 2** below. The device is capable of delivering 125 mcg epinephrine per accuation from the mouthpiece. The dose indicator is a count-down indicator that displays the number of doses left in the canister in 20-dose increments. As the inhaler nears empty (i.e., 20 doses left), the dose indicator displays the remaining number of inhalations in red background to warn users that the inhaler needs to be replaced.

Figure 2: Proposed Product E004



In general, priming is needed for all MDIs. (b) (4) The proposed epinephrine inhalation aerosol product is a suspension. Therefore, proper shaking is required to ensure that suspended particles are uniformly distributed in the product. The epinephrine product is instructed for 4 initial primes (shake and spray into the air in sequence 4 times), one reprime (shake and spray) before each use, and daily cleaning of the mouthpiece (if inhaler is used). The canister has a capacity of 164 sprays, so after the initial 4 primes, 160 sprays remain. Thus, the number of doses (sprays) will be reduced with the proposed reprimes before every use, and the lifetime of the product would be limited to <10 days if used at the maximum rate of 8 inhalations per day. From a clinical standpoint, since the product is intended for temporary, intermittent use, limiting the number of doses in the inhaler is appropriate.

Combined CMC Review was conducted by Danae Christodoulou, PhD, ONDP, DNDP2/Branch IV. His review summarized the reviews of the Quality Review Team (see **Table 1** below).

Table 1: Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Shelly Markofsky	Reviewed during first cycle See DARRTS 4/25/2014
Drug Product	Muthu Ramaswamy	ONDP/DNDP2/Branch VI
Process	Muthu Ramaswamy	Reviewed during first cycle DARRTS 4/25/2014
Microbiology	Bryan Riley	Reviewed during first cycle See DARRTS 7/25/2013
Facility	Carl Lee	OPF-Facilities
Biopharmaceutics	NA	
Regulatory Business Process Manager	Thao Vu	OPRO
Application Technical Lead	Danae Christodoulou	ONDP/DNDP2/Branch VI
Laboratory (OTR)	NA	
ORA Lead		
Environmental Analysis (EA)	Muthu Ramaswamy	Reviewed during first cycle See DARRTS 4/25/2014

Electronically copied and reproduced from Dr. Christodoulou's review.

Dr. Christodoulou recommended approval from CMC perspective. The CMC review concluded that the epinephrine inhalation aerosol is a drug product with similar quality performance as prescription inhalation aerosols (MDIs) containing HFA and that the labeling instructions for use are supported by sufficient CMC characterization data. However, Dr. Christodoulou observed , "because the suspension inherently settles upon standing, shaking and spraying into the air before taking a dose is a critical instruction that the patient needs to understand and perform to receive a uniform dose. Initial priming and re-priming is indicated in similar prescription MDIs, but for prescription products, patients could receive counseling to understand and execute instructions for use (IFU)." Therefore, Dr. Christodoulou writes that "the ability of patients to comprehend and execute these instructions in the OTC setting without counseling and physician supervision is critical to achieve the expected product performance. The suitability of this product for OTC use is deferred to the clinical team's evaluation and the assessment of the human factors studies and label comprehension studies."

Facilities Compliance Status

The Sponsor's response to the CR letter stated that, based on the re-inspection of (b) (4) facility, FDA is now classifying (b) (4) facility as acceptable. This information was reviewed by Carl Lee, facilities reviewer, who concluded that Armstrong Pharmaceuticals, Inc. (FEI: 3007009553) and (b) (4) are acceptable for the manufacture of Epinephrine Inhalation Aerosol USP 125mcg/actuation. In addition, the CDRH-OC reviewer (Francisco Vicenty, Chief, REGO, DMQ, OC, CDRH), issued a memorandum (1 December 2016) for compliance of the device and determined that no pre-approval inspection was required as the recent cGMP inspection of the firm covered elements that demonstrated compliance of the facility and the device. With regards to the documentation

submitted for review, some documentation deficiencies were identified to applicable 21 CFR part 820 regulations for this combination product. Those deficiencies were noted in the review memo for documentation and incorporation into a post-approval inspection assignment.

Drug Product Review

A Drug Product Review was conducted by Muthukumar Ramaswany, PhD, and is summarized below as it provides important information which is relevant to this application. Dr. Ramaswany recommended approval.

Incoming Component Specification for Dose Indiacator Accuracy:

Per FDA advice, Armstrong has revised the component specification used for accepting (b) (4) Dose indicator (Refer to Section 3.2.P.7.2.d) and proposed an AQL of (b) (4) to be used for inspecting this attribute. For count accuracy, dose indicator should reach zero after (b) (4) accuations. AQL (b) (4) allows zero defects and lot is rejected if 1 defective unit found. OPQ concluded that the proposed AQL of (b) (4) for count accuracy is acceptable.

Reliability of Dose Indicator if Dropped:

The original NDA submission contained results from a drop study for *E004 inhalers assembled with actuators* (report # *Final Report for Drop Test for E004 (Epinephrine HFA MDI) Product*; QARD-013-11-00FR. In this study, E004 inhalers (n=90) were dropped from 1 meter height onto concrete floor with Dose indicator (DI) facing down or up or in horizontal orientation. No malfunctioning units were reported in the study. Over counting was observed. No undercounting was noted.

The resubmission contains additional data from a study when 600 E004 inhaler units assembled with or without the actuator were dropped 5 feet from the floor with DI facing down or up or in horizontal orientation. The drop study simulated situations that could occur during routine use of the product or could occur during cleaning and drying of the mouthpiece or when the actuator is removed from the canister. When E-004 units were dropped with actuators (n=600), all units passed the acceptance criteria for visual observation of physical damage, count accuracy, valve and DI force characterization tests, and shot weight accuracy. For the MDI units were dropped without an actuator (n=600), 98.2% units tested (589 units) passed all 5 tests; with 10 units out of 600 (1.67% failure) did not function normally due to breakage of stem or valve and one unit (0.17%) stopped counting due to breakage of DI. Accuracy results showed that 98.8% of the total units did not show any change (remained normal) or showed over counting by 1-3 counts. Remainder of the units (1.09%) showed an increase of 2-3. No undercount was noted.

Shot Weight Analysis (Measure of unit performance):

The dropped units were tested for shot weight after one spray (i.e. re-priming). Weight loss results for 99.2% of the units corresponded to loss due to prime spray + loss due to partial spray. OPQ concluded that the results are consistent with the (b) (4) The revised instructions require the user to

prime the inhaler before each use, and OPQ concluded that this is a very conservative recommendation.

Force needed to actuate the dose indicator and MDI valve (FTA and FTF):

The force to fire (FTA) and force to actuate (FTA) was tested for all units in the study after the drop test. FTA and FTF results were within the expected range for a dose indicator and metering valve. OPQ observed that FTA and FTF results are separated from each other. This is important because if there is significant overlap between FTA and FTF, the potential for the drug indicator to undercount would be implied.

In his review, Dr. Ramaswany noted that, if the inhaler is dropped, there is a possibility that the dose indicator may be damaged and not count properly. He continued, "the drop study results indicated that a total of ten units were damaged due to broken stem and valve (0.8%). All damaged units belonged to E004 units without actuator group. This is expected, as the valve stem (b) (4) component for the chosen and commonly used (b) (4). 1 out of 1200 dose indicator used in the study did not function after dropping, indicating a very low possibility of such occurrence (0.8%). (b) (4)

Effect of variations in mouthpiece cleaning procedures on E004 unit performance:

Dose content uniformity data from the original submission and resubmission indicated that the use of E004 units beyond 2 days of use (8 puffs/day x 2 days) will result in inconsistent dosing due to clogging of the mouthpiece. Based on the initial studies, cleaning the mouthpiece with water and air drying overnight was recommended. The labeling instruction states, "(b) (4) run water through (b) (4) mouthpiece for 30 seconds (b) (4) Air dry overnight." OPQ noted that incomplete drying would result in a wet mouthpiece, which could affect the dose content uniformity of initial sprays. Based on dose content uniformity data, the initial dose may be as much as (b) (4)%. Therefore, the labeling instructions required the user to (b) (4)

The resubmission contains CMC data from additional cleaning studies that evaluated the effect of the following variations to mouthpiece cleaning procedures on the performance of E004 units:

1. Wash frequency (cleaning daily vs. alternate days);
2. Wash direction (up or down or down with water or soapy water. (b) (4)
3. Wash time (2-30 seconds);
4. Water temperature (10, 25, 30, 40, or 50 degrees Celsius);
5. Drying method (air dry, air dry with paper towel, or lint free towel); and
6. Wet unit/re-prime.

(b) (4)

Effectiveness of the cleaning procedure was evaluated per USP dose content uniformity test (n=10 inhalers/test) after single prime. The mouthpieces used for cleaning studies went through two days of simulated use (24 doses dispensed through actuator). Dose content uniformity results indicated that a minimum of 2 second wash gave acceptable results. Dose content uniformity was not impacted by rinse time and rinse water temperature. Air drying overnight was equivalent to quick drying. Based on the study results, the original label instruction was simplified from (b) (4) to "Run water through (b) (4) for 30 seconds; Air dry overnight."

Dr. Ramaswamy noted that if users do not clean the inhaler, the inhaler may become clogged and deliver an incomplete dose and provide incomplete relief of symptoms. Furthermore, if the inhaler becomes blocked, it may stop working. However, Dr. Ramaswamy concluded that the Sponsor's study results "demonstrated that rinsing the inhaler for at least 2 seconds after two days of use will ensure that the inhaler is sufficiently clean." Therefore, "Washing both ends of the mouthpiece daily for 30 seconds is very conservative recommendation." Furthermore, Dr. Ramaswamy concluded that "both air drying and quick drying (dry with paper towel or lint free cloth) can provide acceptable results and thus indicating variations in cleaning/air drying procedures are acceptable."

Dr. Ramaswamy also observed that the proposed cleaning procedure is simpler and easier than the original label instructions for Primatene Mist CFC MDI, as shown in **Table 2** below (electronically copied and reproduced from Dr. Ramaswamy's review). Furthermore, Dr. Ramaswamy noted that many approved products' instructions direct patients to wash the actuator with warm water and let it air-dry completely at least once a week (see **Table 3**) and in this case, the Sponsor is instructing the user to clean daily (b) (4)

Effect of improper initial priming on dose content uniformity of initial sprays:

In the original submission, the Sponsor provided data to support the need to prime the MDI unit before use. The Sponsor also provided data to show that a (b) (4) . Dr. Ramaswamy noted that inhaler not shaken before use may dispense a super potent dose (~ (b) (4) %), and that results indicated that bulk suspension may partially separate and settle in the canister and cause non-uniformity. Therefore, the user is required to perform priming (shake and spray) prior to first use of the device and before each use. Per labeling instructions prior to first use, the user is required to shake and spray into the air, then repeat this sequence three more times.

The Sponsor has simulated scenarios when patients did not follow instructions in the resubmission. Failure to properly complete this prime sequence (Shake and spray sequence 4 times) may result in the user receiving a slightly higher or lower dose of medication for the first several sprays. For example, if a patient shakes the MDI unit once and dispenses 4 priming sprays in succession rapidly (i.e when entire effort is completed in 2-10 seconds) or very slowly (i.e when entire effort is completed in 30 seconds), it may result in dispensing of non-uniform dose. Furthermore, users who never prime the inhaler throughout the life of the device could continue to receive inconsistent dose.

The resubmission contains data from such a simulated use study. The results are liiustrated in **Figure 4** below (electronically copied and reproduced from Dr. Ramaswamy's review):

(b) (4)

Dr. Ramswamy observes that dose content uniformity (DCU) results for the initial sprays dispensed from canisters with long execution time (15-30 seconds for completing 4 sprays) indicated a high probability that the initial first two doses will be super potent, a maximum of (b) (4)% of labeling claim (LC) and will be outside acceptance criteria of (b) (4)% LC . The Sponsor has rationalized that this (b) (4)% dose from a single actuation is within permitted daily dose limit. The Sponsor has also rationalized that the super potent dose (b) (4) during the 30 seconds of priming, (b) (4)

Quick dispensing of the 4 priming sprays (2-3 seconds) also resulted in a lower % label claim recovery (< (b) (4)% for 2 out of 9 devices). Dispensing of the 4 priming sprays within 4 -12 seconds resulted in acceptable dose content for the sprays. The Sponsor has rationalized the lower DCU results obtained from quick priming step (4 consecutive sprays dispensed in 2 seconds) as due to the following: (b) (4) The Sponsor also noted that if the potency of first spray is low and did not relieve the symptoms, the user can inhale a second spray as long as it does not exceed the maximum dosing limits. The dose content uniformity results through canister life are shown in the following graph (**Figure 5**; electronically copied and reproduced from Dr. Ramaswamy's review). (b) (4)

(b) (4)

(b) (4)

Dr. Ramaswamy concluded that the Sponsor "has adequately investigated the failure modes associated with improper priming," and Dr. Ramaswamy agreed with the Sponsor's assessment that failure to properly complete the priming (shake and spray 4 times) sequence may result in the user receiving a sub or super potent dose for the first two sprays. Dr. Ramaswamy wrote, "the users who never prime the inhaler throughout the life of the device could continue to receive inconsistent dose. It is expected that the fully primed or re-primed unit will deliver a full concentration of medication during initial use and during inhaler life."

Dr. Ramaswamy also noted that "user instructions for approved MDI suspension products require priming the inhaler prior to first use." However, "it is not typical for approved products that the user is required to prime the device by shaking and spraying into the air one time before each use." See **Table 3**. Nevertheless, Dr. Ramaswamy observed that the proposed labeling instructions are either typical or more conservative than for currently approved products, and the Sponsor's repriming instructions to shake and spray into the air 1 time prior to each use is a very conservative recommendation."

Table 3: Comparison of Priming Instructions between Epinephrine HFA Product and Other Prescription HFA Products

NDA #	Product Name	Initial Priming	Formulation	Reprime frequency	Shake	Reprime	Dosage	Cleaning of mouthpiece
205920	Trade Name (epinephrine inhalation aerosol)	4	HFA 134a + epinephrine+ 1% ethanol	Before each use	-	1	Suspension	Daily
20983	Ventolin HFA (albuterol sulfate) inhalation aerosol	4	HFA 134a + albuterol sulfate	2 weeks	-	4	Suspension	Once a week
21457	ProAir HFA (albuterol sulfate) inhalation aerosol	3	HFA134a, albuterol sulfate, and ethanol	2 weeks	-	3	Suspension	Once a week
21433	Flovent HFA (fluticasone propionate) inhalation aerosol	4	HFA + drug	1 week	5 sec	1	Suspension	Once a week
22518	Dulera -(Mometasone Furoate and Formoterol Fumarate)	4	HFA + mometasone furoate and Formoterol fumarate	5 days	-	4	Suspension	Once a week
208294	Bevespi Aerosphere (glycopyrrolate and formoterol fumarate) inhalation aerosol	4	HFA + glycopyrrolate and formoterol fumarate + phospholipid	7	-	2	Suspension	Once a week
21254	ADVAIR Diskus (Fluticasone propionate)	4	HFA + drug	4 weeks	5 sec	2	Suspension	Once a week
21658	Alvesco (ciclesonide) inhalation aerosol	3	HFA + drug + ethanol	10 days	Not needed	3	Solution	Once a week

Another potential issue identified during Failure Mode Effect Analysis (part of the Human Factors Engineering Study) was that improper holding of the canister during actuation (off center actuation) could cause the canister to tilt to the side and would release additional medication through the valve stem. The Sponsor mitigated this risk by the design of the actuator system, including, for example, addition of a concentric ridge on top of the dose indicator to improve the grip and thus reduce the likelihood of the user's fingers slipping and pushing sideways.

(b) (4)

In conclusion ,Dr. Ramaswamy wrote, "overall, the applicant has investigated potential deviations to priming and cleaning instructions. The proposed labeling instructions are reasonable and consistent instructions with that available for other approved metered dose inhalers."

CDTL Comment: I agree qith OPQ assessment and conclusions. Howeevr, from clinical standpoint, whether or not consumers can adequately understand and follow the IFU in order to properly administer the product, is a separate issue which will be addressed in the sections to follow.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review (**Pharmacology/Toxicology NDA Review and Evaluation**; 16 November, 2016) was conducted by D. Charles Thompson, RPh, Phd, DABT. From nonclinical standpoint, Dr. Thompson recommended approval. He wrote, "The chronic inhalation toxicity studies described by the Sponsor in the original NDA resubmission fail to meet generally accepted scientific and regulatory standards for study design and conduct. However, taking into consideration all original and subsequent information that the Sponsor has submitted, in conjunction with all other available safety information on thymol and the low clinical exposure levels anticipated, the proposed clinical use level of (b) (4) % thymol as an excipient appears to be reasonably safe from a nonclinical perspective." He also noted that this decision "is pending a final reporting from the OSIS GLP inspection of the nonclinical test facility," which was not complete at the time.

A primary deficiency identified in the CR action was a lack of nonclinical safety support for the proposed formulation excipient, thymol, under chronic inhalation conditions for use. The CR letter stipulated that this deficiency must be addressed by submission of a 6-month repeated dose inhalation toxicity study in an appropriate nonclinical species.

The current submission includes a single, summary report of two parallel, overlapping 6-month repeated dose inhalation toxicity studies in CD-1 mice, plus results of a separate toxicokinetic (TK) analysis in mice under comparable exposure conditions but conducted approximately 1.5 years after the chronic studies. In his review, Dr. Thompson notes that a study protocol for the inhalation toxicity study was submitted to DNDP for comment but not until approximately 2-3 months after both studies had been initiated. An Information Request (IR) was sent to the Sponsor on 4 November 2016 that included a request for individual study reports for each of the three conducted studies. However, the response received on 9 November 2016 indicated that separate reports do not appear to exist for the two 6-month toxicity studies, as the decision to merge these two studies occurred while the two studies were ongoing. A separate PK study report was included in the IR, and Dr. Thompson writes that, "these data appear to be consistent with those submitted in the original NDA submission."

Dr. Thompson concludes that, on face, "the study data provided suggest an absence of either local or systemic adverse effects in mice following repeated inhalation exposure for six months. However, … the study design employed suffers from a number of significant deficiencies based on review of published literature and national and international nonclinical testing guidelines." These deficiencies include the following:

- Exposure chamber aerosols were not continuously generated throughout duration of animal exposures.
- No concurrent and repeated assessment of exposure chamber concentrations.
- No concurrent and repeated assessment of exposure aerosol APSD (aerodynamic particle size distribution).
- No continuous airflow through the exposure chambers; humidity and oxygen concentration were not monitored and reported.
- Exposure duration of 10 minutes/day, 3 days/week is less than the maximum feasible duration and frequency.

- Number of animals (8/sex/group) is less than optimal.
- Respiratory parameters including respiratory rate, minute volume and tidal volume were not measured.
- Blood gas parameters pO2 and pCO2 were not measured. Blood pH was not measured.

Dr. Thompson reports that, due to the lack of concurrent sampling of the chamber air for thymol during animal exposure, it was difficult to determine if animals were being exposed to a concentration of thymol higher than the clinical formulation (b) (4)% thymol). The Sponsor's air sampling showed that there was a loss of 57% to 71% of the nominal dose of thymol. (b) (4) FDA requested data characterizing the physical state of thymol in the chamber, the amount of thymol discharged from the MDI, and the Sponsor's assay for thymol discharged from the MDI (IR; 25 August 2016). The Sponsor provided data showing that recovery rate was 0.8% to 2.9% for particulate thymol, (b) (4) . This appeared to support the Sponsor's assumption that thymol was not found as a particulate, but did not eliminate the original concerns regarding the amount of thymol discharged from the MDI. (b) (4)

On 4 November 2016, the Sponsor was asked to characterize the amount and physical state of the thymol discharged from the MDI. The Sponsor provided further data on 9 November 2016, using MDI formulations with (b) (4)% thymol. The analytical methods and results in the study titled "Final Report for The Amount of Thymol per Actuation Studies" (study # QARD-029-16-00FR) were assessed by CMC reviewer Dr. Muthu Ramaswamy and determined to be reasonable (verbal communication, 9 November 2016). The study had two parts, designated DCU-1 and DCU-2. Study DCU- 2 showed that the amount of thymol discharged from the MDI was within acceptable range using the dose content uniformity method (based on USP <601>). Importantly, this showed for the first time that the Sponsor could recover the expected amount of thymol expelled from their MDI when spraying the formulations used in the nonclinical study.

Study DCU-1 provided supportive evidence of thymol being expelled in a vapor state. The proposed MDI was used to spray the formulations used in the nonclinical study, and a vacuum pump was used to remove all vapor/gas phase material. The collection tube and filter were assayed for thymol, and showed a recovery rate of 3.6% with (b) (4)% thymol, and 3.2% with (b) (4)% thymol. By simple mathematical extrapolation, (b) (4)

Thus, in his review, Dr. Thompson wrote, "Based on these newly submitted data suggesting that the amount of thymol expelled from the MDI was, as designed, notably greater than the clinical dose, in conjunction with the levels of thymol detected in the animals in the ad hoc PK study, it is reasonable to conclude that the animals were substantially exposed to thymol in a vapor phase." He continued, "Assuming the loss of 57% at the high dose of (b) (4)% thymol, vaporous thymol at the animal breathing zone in the exposure chambers may have been as much as 0.3%.

Based on the clinical concentration of (b) (4)% thymol, animals would thus have been exposed to up to (b) (4)-fold higher concentrations of thymol."

Dr. Thompson noted, however, that in assessing the overall safety of the proposed level of (b) (4)% thymol, the limited amount of thymol exposure expected (approximately (b) (4) µg/day) and the previous human experience with thymol were taken into consideration. Therefore, Dr. Thompson cautioned that "future proposed products with higher levels of thymol exposure should be supported by more robust inhalation data with thymol."

Dr. Thonpson concluded that "in consideration of the totality of the information described above, the proposed amount of thymol in the clinical formulation is considered to be safe from a nonclinical perspective for the indication of temporary relief of mild symptoms of intermittent asthma. This decision is pending a final determination as to the GLP-compliance of the nonclinical test facility and inspected studies."

GLP Inspection:

A FY2016 GLP directed inspection of the study site (Amphastar Laboratories; Chino, CA) was conducted by: LCDR Marcus F. Yambot, Investigator, ORA/LOS-DO; Ke Zhang, PhD, CDER Pharmacologist; and Zhou Chen, MD, PhD, CDER Pharmacologist. The studies audited were the nonclinical studies described above and as summarized in **Table 4** below (electronically copied and reproduced from Dr. Chen's review (**Pharmacologist Review of GLP EIR (CP 7348.808)**).

Table 4: Studies Audited During this Inspection

Study Number	E004-VO-002	E004-VO-003	E004-VO-005
Study Title	Chronic Toxicity of Thymol on Lung and Respiratory Tract	Chronic Toxicity of Inhaled Thymol in Lungs and Respiratory Tracts in Mouse Model	Pharmacokinetic Study of Thymol after Intravenous Injection and High-Dose Inhalation in Mouse Model
Test Article	Thymol		
Sponsor	Armstrong Pharmaceuticals		
Study Director	Kevin Xie, PhD		
NDA Number	205920		
Review Division	DNDP		
Study Initiation	09/10/2014	10/09/2014	5/9/2016
Study Finalization	7/10/2015 (with study E004-VO-003)	7/10/2015	6/28/2016

A summary of their observations includes the following:

(b) (4)

Overall, Dr. Chen concluded, "the final classification for this inspection is Voluntary Action Indicated (VAI)." He continued, "After evaluating the inspectional findings, the data from the three audited studies were found to be unreliable. Therefore, the three audited studies should not be considered GLP-compliant studies and the data should be considered for reference purposes only."

Nonclinical Pharmacology/Toxicology Secondary Review

In view of Dr. Chen's conclusions in conjunction with Dr. Thompson's assessment that the proposed clinical use of thymol appears to be reasonable safe, pending results of the nonclinical site audit, a secondary review was performed by Jane Sohn, Ph.D., Pharmacology/Toxicology Team Leader, DNDP. Dr. Sohn conducted further discussions with Dr. Chen and clarified that no fraudulent activities were found, although the clinical observations in the study were unreliable. Importantly, the tissue collection and pathological samples were handled in a reliable manner. Dr. Chen did not recommend that the study be rejected and supported using the nonclinical data in combination with clinical data for safety assessment. In conclusion, Dr. Sohn wrote, :this NDA can be approved from the pharmacology/toxicology perspective and no additional nonclinical studies are needed. The decision relies upon the available nonclinical data, in combination with previous human experience reviewed by the clinical team."

CDTL Comment: I agree with Dr. Sohn's assessment. It is important to note that the integrity of the tissue collection and pathological samples is not in question. The absence of histopathological findings in these nonclinical studies in conjunction with the well-characterized clinical safety profile of epinephrine inhalation aerosol is adequate to conclude that the proposed clinical use of thymol is reasonably safe.

5. Clinical Pharmacology

No clinical pharmacology data or studies was submitted with this Complete Response. During the first cycle, the Clinical Pharmacology review and recommendation of 'acceptable' was finalized on 9 April 2014. It is noteworthy that, upon inhalation , the drug is only minimally absorbed, having its effect primarily on beta receptors in the respiratory tract within 1-5 minutes.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No clinical efficacy data was submitted with this Complete Response. The results of 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 Review of Jennifer Pippins, MD, MPH; Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), dated 14 April 2014. Regarding efficacy, Dr Pippin concluded that "the clinical program provides evidence of the proposed product's efficacy as a bronchodilator."

8. Safety

No clinical safety data was submitted with this Complete Response. In the first cycle, safety data from the clinical trials was reviewed by Ryan Raffaelli, MD; Division of Nonprescription Drug Products (see Dr. Raffaelli's Review dated 15 April 2014). Dr. Raffaelli also reviewed marketing experience from 1997-2012 for Primatene Mist (former manufacturer [Wyeth] pharmacovigilance database, FAERS, data from American Association of Poison Control Centers, and published literature).

Importantly, consultation was obtained with the Division of Cardiovascular and Renal Products (DCRP) to assess cardiovascular safety of the product, and the results of two high dose pharmacokinetic trials were reviewed. Several pharmacodynamic safety measures indicated that resultant drug levels at doses nearly 13-fold higher than proposed (125 mcg versus 1600 mcg in one trial) were not likely associated with significant safety issues, i.e., transient hyperglycemia, hypokalemia, increases in blood pressure or heart rate, or arrhythmias. There was no data identifying a cardiovascular safety concern when the product was used as intended,that is, according to labeling. Dr. Raffaelli concluded that, "overall, the data, including cardiovascular data, were supportive of safety of an epinephrine inhalation aerosol available in the OTC setting."

9. Advisory Committee Meeting

No Advisory Committee (AC) Meeting occurred 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 25 February 2014. For a detailed summary of the AC meeting, see Dr. Raffaelli's review.

10. Pediatrics

The Sponsor proposes labeling for use of this product by adults and children as young as 12 years of age. The original Primatene Mist CFC product was not approved for use by children under age 4 due to safety concerns. During the first review cycle, it was noted that a 4-week efficacy trial was completed in children 4-11 years of age. The data from this trial did not support efficacy in this age group; however, the study was very small (N=8).

This product triggers PREA as a new dosing regimen. In the current Complete Response, the Sponsor submitted a pediatric plan seeking a partial waiver consistent with FDA's prior determination that the product is not appropriate for children under age 4. (b) (4)

(b) (4)

Sofia Chaudrey, MD, Division of Pulmonary, Allergy, and Rheumatology Products revieed the proposed pediatric plan (b) (4)

The proposed pediatric plan was discussed at a Pediatric Research Committee (PERC) Meeting on 16 November 2016. The PERC recommended that the Sponsor (b) (4) PERC recommended that PK data be obtained as part of the clinical trial. PERC agreed to the waiver in children less than 4 years of age and to a deferral in patients 4-11 years of age.

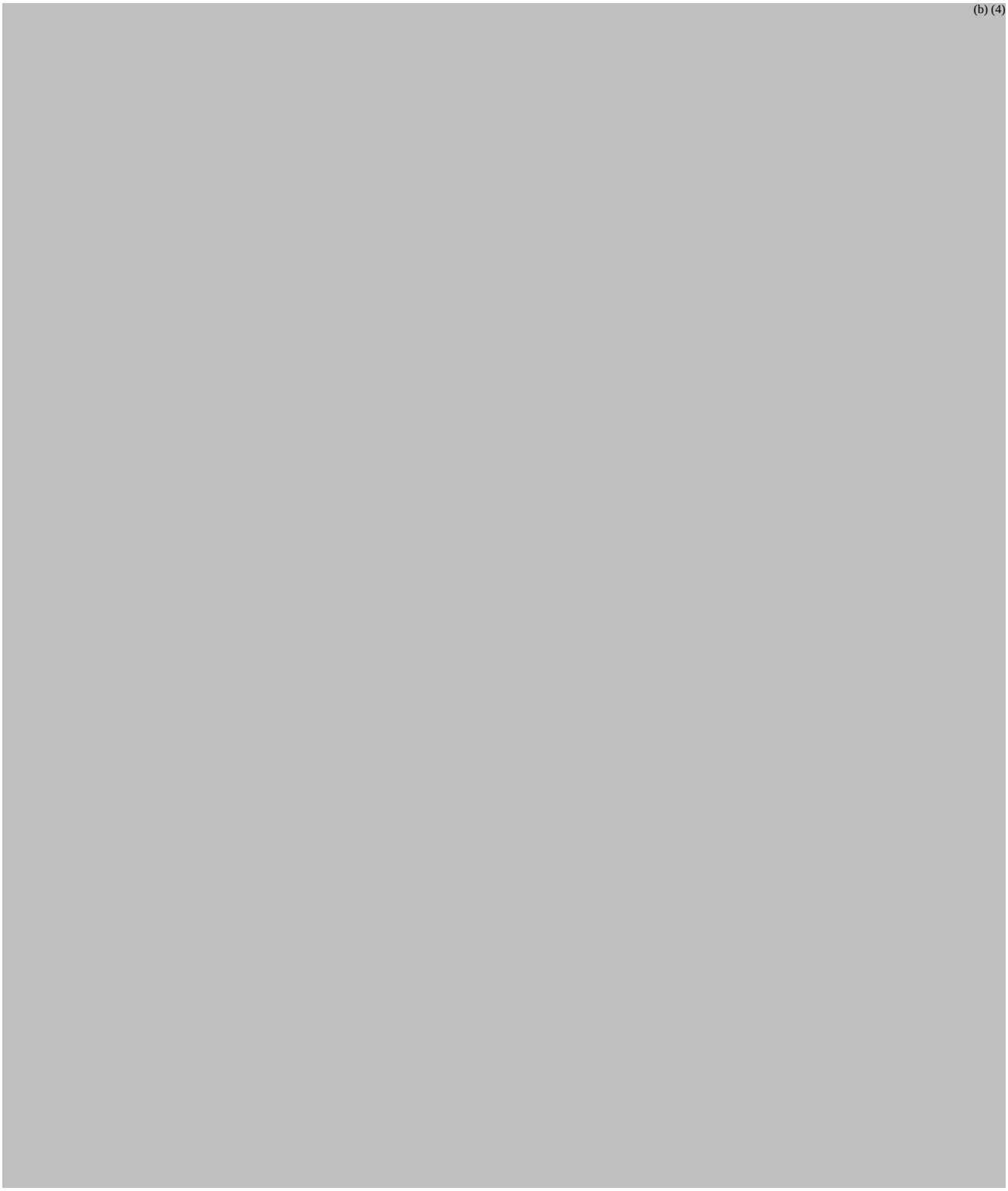
11. Other Relevant Regulatory Issues

No additional relevant regulatory issues have been identified during this review cycle.

12. Labeling

An example of the Sponsor's proposed labeling is shown in **Figure 6** below, and the Sponsor's proposed Instructions for Use (IFU) is shown in **Figure 7** below (both figures are electronically copied and reproduced from DMEPA review):

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



As noted above, the Sponsor originally submitted NDA 205920, as a 505(b)(2) application for a reformulation of Primatene Mist, on July 22, 2013. Three label comprehension studies (I, II, and III) and one human factors study were included in the NDA (see Social Science Review dated April 23, 2014). The application was also discussed at a joint meeting of the Nonprescription

Drugs Advisory Committee (NDAC) and the Pulmonary Allergy Drugs Advisory Committee (PADAC) on 25 February 2014, where FDA (DPARP) presented its concerns about the device performance, given the relatively high number of device malfunctions and dose indicator errors presented in the clinical studies. The Complete Response letter to the Sponsor cited the high number of device malfunctions in the clinical trials, including apparent user errors with the dose indicators and also with clogging. Furthermore, the results from the label comprehension studies and the human factors study supported these usability issues, demonstrating that there were limitations in consumers' understanding of critical information such as: not relying on the dosing indicator if dropped; the need to prime the indicator before using the first time; the need to clean the product daily after use; and the need to re-prime when wet.

Social Science Review

In support of this Complete Response, the Sponsor conducted three label comprehension studies (LCS IV, V, and VI) which were reviewed by Barbara Cohen, MPA, Social Scientist, DNDP. Ms. Cohen noted that none of the studies were able to demonstrate that low literacy subjects had good comprehension of all the circumstances under which they needed to prime the product prior to use. Ms Cohen also noted that, subsequent to conducting the three label comprehension studies, the Sponsor significantly revised the Instructions for Use (IFU) to simplify and clarify the priming instructions as well as other aspects of labeling. (b) (4) The revised labeling was streamlined to introduce simplicity and clarity in the IFU. (b) (4) the labeling simply states (b) (4) The revised labeling was then tested in human factors studies, which were fielded approximately a year after the final LCS. The Sponsor also simultaneously conducted bench testing that further refined its benefit/risk analysis relevant to LCS and human factors findings. Ms. Cohen concluded that the human factors findings are more relevant than the LCS, given the significant changes to the label post-LCS, and that the bench studies are more relevant for approval as they provide context for the Sponsor's benefit/risk assumptions. The Human Factors Engineering Report (G3) is reviewed by DMEPA (see below); however, Ms Cohen cited relevant aspects of this report in her review.

All three studies were single visit studies of similar design and size, varying somewhat in demographics. All primary communication objectives were designated as primary endpoints of significant risk based on comments received on May 22, 2014 from FDA and were assigned a target performance threshold of 85% in keeping with previous label comprehension work conducted. The primary objectives and secondary objectives varied somewhat between studies, presumably based on findings from the preceeding studies. For a detailed review of LCS IV, V, and VI, please see Ms Cohen's Social Science Review. Important aspects of the study designs and results are outlined below.

Label Comprehension Study IV:

In response to key findings from LCS III, the Sponsor determined that the following insert changes were needed and would be the focus of LCS IV:

- (b) (4) section to clarify that there are new user instructions.
- An (b) (4) section" added to address issues of the Advisory Committee.
- Modification of the priming section, including the addition of "shake (b) (4) spray."
- Additional visuals to assist in communication important concepts.

In LCS IV, comprehension of the following as primary objectives was addressed:

1. Wash the mouthpiece daily if used.
2. Prime before first use.
3. Prime the inhaler again if it is:
    a. Wet
    b. Dropped
    c. Not used for (b) (4) days
4. Place fingers on center of dose indicator.
5. Instructions for removing the canister for cleaning mouthpiece
6. Chidren under 12 years of age; do not use.
7. Do not use more than 8 inhalations in 24 hours.
8. See your doctor if you have more than two asthma attacks in a week.

Regarding the primary objective, "Prime before first use," the Sponsor subsequently deleted this objective from the study during the development of the data collection instrument and asserts that it was determined at the time that this objective would be most appropriately addressed in a human factors study. However, as noted by Ms. Cohen, the Sponsor apparently changed its mind and decided to assess this primary objective in LCS V.

In addition, the following secondary objective was assessed:

1. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take.

This secondary objective was assessed at a 75% threshold and categorized as a secondary objective because, according to the Sponsor, although it was initially theorized in the first NDA submission that the risk of damage to the dose indicator if dropped was high, the results of subsequent exhaustive drop tests (Study QAPO-006-14-00-FR) demonstrated that the dose counter never had any critical malfunction. However, Ms. Cohen noted in her review that the currently proposed Instructions for Use (IFU) include, as (b) (4) which would seem to contradict its characterization as a secondary objective.

In this study, 506 completed interviews took place. There was good Hispanic representation at 14% with fairly good low literacy representation at 25%.Approximately 14% of the sample reported suffering from asthma, with a slightly higher proportion among low literacy than normal

literacy participants. The Primatene Mist user cohort included only 36 participants (7%) but demographic characteristics were not significantly different than the non-user cohort.

The normal literacy (NL) population achieved high levels of comprehension for most communication objectives and, for the low literacy (LL) population, comprehension of the need to wash the inhaler daily when using it was 91%, with 85% lower bound (LB). However, low literacy comprehension of "Prime the inhaler again if it is wet, dropped, or not used for more than two days" was 81% for wet (LB of 73%) and 65% for wet, dropped or not used for more than two days (LB of 56%). This may be of particular concern because, if the inhaler is not properly primed, it may not work effectively. As the G3 Engineering Report states, "*during the priming process, shaking of the inhaler ensures that the medication is evenly mixed and distributed throughout the canister. If the step is not performed (neither shaking nor spraying), it could create an uneven distribution of the medication and ingredients during the subsequent actuation, such that the product may not provide a full dose during the inhalation. If the user does not perform priming a total of four times, the subsequent uses of the product may not provide full doses during the inhalation."*

In addition, the communications objective of "Place your finger on the center of the dose indicator" achieved a low literacy comprehension score of 84%, with a 77% LB. As noted in the G3 Engineering Report, if the user's finger is offset, the canister could be pushed sideways and not directly downward; the tilting to the side could release additional medication through the valve stem, resulting in less medication remaining in the canister than accounted for in the dose indicator. With continued use, this could result in the dose indicator showing actuations left when there is no medication in the canister.

Lastly, "do not rely on the dose indicator if dropped" had a low literacy comprehension score of 85%, with a LB of 77%. The Sponsor determined this to be a secondary objective, and subsequent bench testing determined that this was a low risk issue. Therefore, this objective was not retested in LCS V and VI.

Former Primatene users performed worse on most questions compared to non-users. However, the cohort was small – only 36 users compared to 469 non-users. Former users seemed to have the most difficulty with the concept of priming. Ms. Cohen noted that, since former Primatene users also tended to be low literate more so than non-users, this could have been a factor in the results.

Furthermore, comprehension scores for "do not use more than 8 inhalations in 24 hours" were good for normal literacy but 89% for low literacy, with a 82% LB. Ms Cohen suggests that this statement may need to be highlighted in the DFL, and she opines that this would also reinforce the concept that the indication is for mild symptoms of asthma only.

Label Comprehension Study V:

Based on the results of LCS IV, the following product insert design changes were instituted to be evaluated in LCS V:

1) Addition of a key to determine when 4 or 1 Prime (Shake and spray) are needed,
2) Addition of a safety alert symbol (triangle and exclamation mark) to draw attention to the prime (shake and spray into air) bulleted information,
3) Removal of the shake off excess water instruction from the Wash the Mouthpiece Daily if Used section, and
4) Addition of product color to the illustrations.

In LCS V, comprehension of the following as primary objectives was addressed:

1. Prime before first use
2. Prime the inhaler again if it is wet
3. Prime the inhaler again if it is not used for 2 days
4. Place fingers on center of dose indicator

The Sponsor provided detailed clinical justifications for the target threshold relative to priming before first use. The Sponsor states that the target performance threshold of 85% is appropriate given the minor clinical risk of not receiving a full dose of medication for the first few doses as a result of failing to understand this instruction. The Sponsor states that multiple priming (i.e. four times) of the inhaler is only required for the initial use of the inhaler. Failure to perform the initial priming results in insufficient drug delivery for only the first few uses. Subsequent sprays are not impacted. Furthermore, the Sponsor notes the DFL instructs users to "see a doctor if you are not better in 20 minutes." Thus, if a user does not improve after 20 minutes (b) (4) he or she would still be advised to seek medical attention.

However, Ms. Cohen states in her review that the Sponsor's "rationale is not clear for two reasons." First, it uses the term "priming" without parsing it for the two separate steps of shaking and spraying. In the LCS, the Sponsor did not assess comprehension of what "priming" meant. Therefore, Ms Cohen notes that the Sponsor seems to be implying that whether a consumer only shakes, or only sprays, or only shakes and sprays once for initial priming, such actions are equivalent in that they would only impact the first few uses and afterwards dosing would be correct. Ms Cohen reviewed five of the human factors study videotapes (discussed below) which showed that subjects did not always shake *and* spray, even with the revised IFU.

Second, Ms Cohen notes that the rationale seems to imply that even if a consumer fails to receive an adequate first dose, this wouldn't be an issue as anyone using it would only have mild symptoms of intermittent asthma, so that they would be in a position to understand to contact a healthcare provider if they still had difficulties after 20 minutes. Ms Cohen defers to clinical reviewers to address this issue.

In LCS V, there were a total of 492 completed interviews. Hispanic representation was poor (6%), and low literacy subjects were slightly under-represented (25%). Approximately 18% of the sample reported suffering from asthma, with a slightly higher proportion among low literacy than normal literacy participants. The Primatene Mist user cohort included only 25 participants (5%) but demographic characteristics were not significantly different from the non-user cohort.

The normal literacy population achieved good comprehension for "prime before first use (92%, 89% LB) and "place finger on center of dose indicator" (93%, 90% LB), and scored at 89% (85% LB) for "prime when wet." However, "prime if not used for two days" scored 87% with LB of 83%, which Ms. Cohen considers to signal difficulty with label complexity.

The LL population performed poorly, with scores of 75%, 75% and 69% respectively for the priming objectives of prime initially, prime when wet, prime if not used for more than two days. The LB was in the 60-70% percentile for all priming objectives. Moreover, as in LCS IV, "place finger on the center of the dose indicator " did not do well, achieving a score of 86% with LB of 78%.

Once again, former Primatene users scored much lower on comprehension of all objectives compared to non-Primatene users.

Regarding the low literacy score of 75% for priming before first use, the Sponsor stated in Response to IR that *"Armstrong does not believe that this result (ie, 75% comprehension) is a true representation of the low literacy population's comprehension of this objective because low literacy subjects were able to successfully demonstrate the behavior of priming the inhaler before first use in study G3. The Applicant believes that the lower scores observed for the low literacy participants on this issue were largely due to the vagueness required of the question asked, which was intended to ensure that the participant was not 'led' to provide a correct answer. Question 1 (regarding prime before first use) from the LCS was as follows: 'Brenda just purchased* (b) (4) *What does she need to do to get a new inhaler ready to use?'* " Ms. Cohen agreed with the Sponsor that the question in the study was problematic and poorly worded. However, she notes that it is unclear the question couldn't be reworded to simply read, *"Brenda is having an asthma attack and is about to give herself a dose of Primatene. What does she need to do first?"*

Label Comprehension Study VI;

Based on the results of LCS V, the formatting of the package insert IFU was changed for the Prime (Shake and Spray into air) the Inhaler Again subsection to increase user recognition.

In LCS VI, comprehension of the following as primary objectives was addressed:

1. Prime the inhaler again if it is wet
2. Prime the inhaler again if it is not used for 2 days.

In her review, Ms Cohen points out that, although initial priming failed to do well with low literacy participants in LCS V, the Sponsor did not test this objective in LCS VI and asserted that, "comprehension had already been successfully demonstrated in LCS II, III, and V." However, Ms. Cohen questioned the Sponsor's assertion, noting that in LCS II and III, initial priming was an informational objective only, that is, the Sponsor assigned no critical importance to it, and the associated question asked only *how many times* the inhaler needed to be primed before first time use. Furthermore, Ms. Cohen notes an assumption was made that participants

had existing knowledge about *the need* for priming. Consequently, no question asked about *the need* for priming.

In LCS VI, there were a total of 485 completed interviews. There was good Hispanic representation at 13%, but poorer low literacy representation (20%) compared to LCS IV and V. Approximately 17% of participants reported suffering from asthma, with a slightly higher proportion amoung low literacy compared to normal literacy participants. The Primatene Mist user cohort included only 31 participants (6%); however, demographic characteristics were not significantly differetnfrom the non-user cohort.

Although the normal literacy population scored well on the priming objectives, the low literacy population did not score well. Comprehension of "prime the inhaler again if it is wet" was 86%, with a LB of 77%, and comprehension of "prime the inhaler again if it is not used for two days" was 80%, with a LB of 70%. Ms. Cohen points out that once again, former Primatene users had lower comprehension than Primatene nonusers, as shown in **Table 6** below.

Table 6: LCS VI Reported Findings

Primary Objective	Question # and Text	Normal Literacy (95% CI) N = 387	Low Literacy (95% CI) N = 98	Users (95% CI) N = 31	Non-Users (95% CI) N = 454	Asthma Sufferers (95% CI) N = 84	Non-Asthma Sufferers (95% CI) N = 401	Total (95% CI) N = 485
1. Prime the inhaler again if it is wet	*Question 1: John cannot let his inhaler dry overnight and must use it when it is still wet. What does the package insert say John should do if he needs to use it when it is still wet?*	93% (90%, 96%)	86% (77%, 92%)	90% (74%, 98%)	92% (89%, 94%)	93% (85%, 97%)	92% (88%, 94%)	92% (89%, 94%)
2. Prime the inhaler again if it is not used for 2 days	*Question 2: Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?*	92% (89%, 95%)	80% (70%, 87%)	84% (66%, 95%)	90% (87%, 93%)	89% (81%, 95%)	90% (86%, 93%)	90% (87%, 92%)

Electronically copied and reproduced from Ms Cohen's review.
Source: Narrative Response to the Statistical Information Request dated September 6, 2016

Human Factors (Study G) Videotapes;

Since the low literacy findings about priming were less than optimal, Ms. Cohen reviewed several of the subsequent human factors study videotapes of low literacy asthma adult users "to obtain qualitative insights as to these findings." In the human factors study, which will be discussed in more detail below, each subject was provided with the revised, streamlined IFU and asked to read it while the interviewer left the room. When the subject had finished reading the IFU, s/he summoned the interviewer to return. The subject was then asked to demonstrate various aspects of using the product. Although Ms. Cohen reported that all of the subjects read the IFU to some extent, she observed the following:

- Subject (b) (6) did not prime before initial use or re-use, and he did not understand how the dose indicator worked. According to the G3 Engineering Report, "*he was an inhaler experienced participant who struggled to read the instructions and was likely not fully functionally literate...he did not recognize a number of words used in the IFU. Throughout the session, he responded to several different questions about the inhaler saying that he simply could not find the information in the instructions...he frequently referred to what he does with his own inhaler*."
- Subject (b) (6), a former Primatene user, did not spray when priming either for initial use or repeat use. None of the asthma products he has used involve spraying. He also stated that he would not want to spray a lot as that would use up medicine.
- Subject (b) (6), a former Primatene user, primed by shaking and spraying once. This subject did not understand how the dose indicator worked.
- Subject (b) (6) primed initially by holding the product horizontally, with middle finger near/on dose indicator. This subject eventually demonstrated use with vertical hold, but still appeared not to be pressing on center of dose indicator. This subject also had difficulty pulling the top out to wash the product, and didn't understand the dose indicator.
- Subject (b) (6) appeared to have a product that did not come fully assembled out of the box, although the extent of the problem was unclear.

In response to an IR regarding Subject (b) (6), the Sponsor explained that (b) (4) [redacted] The Sponsor also stated that it reviewed all of the study videos after receiving the IR. Four of 151 videos were not available due to technical issues, and two additional videos "did not capture the removal by the participant of the product from the carton." Of the 145 participants for which a video was available, the device was not assembled (ie, canister was not secured in the actuator) for five, or 3.4% (5/145) study participants. The Sponsor asserts that all were able to effectively reposition the canister into the actuator, and concludes that in any case this separation was an artifact of Study G3 and will not occur in the commercial product.Ms. Cohen defers to CMC as to whether the Sponsor's explanation is acceptable.

Web-based Labeling:

Ms Cohen also reviewed the Sponsor's submitted website draft. The Sponsor had previously reported to FDA in an April 14, 2014 correspondence that "*although a telephone number is currently provided under Drug Facts, a dedicated website is currently under development in*

order to provide consumers with an additional resource should questions arise. The website will allow 24 hours a day/7 days a week access for consumers with questions regarding the proper use of the product." In a July 22, 2016 IR response, the Sponsor clarified that there was a website link in the DFL. The sponsor stated that the website content was under development and committed to providing a draft of the website content in mid-August, 2016 (after the start of the review cycle). The subsequent website draft was submitted by the Sponsor on August 17, 2016 and contains:

- the DFL and the IFU.
- a summary page highlighting the changes between the current and previous formulations..
- an "Asthma Learning Center"
- Four instructional videos – one each on preparing the product for use, dosing the product, washing the product, and the dose indicator.

The summary page entitled (b) (4) highlights the changes between the old and new formulations. However, it states that the (b) (4) indicator "*shows how many sprays of medication you have left in the container*." It does not indicate that that the dose indicator does not move with every spray. Therefore, Ms Cohen considers this to be a misleading statement which should be revised.

Ms Cohen also reports that the Asthma Learning Center "is highly informative and educational with regard to asthma triggers" and "would probably be helpful to many sufferers." However, she continues, "my concern about the Center is that while it states up front that asthma is a serious disease that should be diagnosed by a doctor, there is little discussion of the potential necessity of some kind of physician monitoring on an ongoing basis (other than reference to an Asthma Plan, which is not defined) and no discussion or definition of what the labeled indication of "mild symptoms of intermittent asthma" actually means. Ms. Cohen continues, "At the very least, the (b) (4) section should be positioned up front and center, instead of at the end. As page 15 of the G3 Engineering Report states, there is no expectation on the part of the Applicant that users of the product will be under the care of a healthcare professional for their intermittent asthma. If that is the case, while the availability of this product may provide a workable solution for those consumers who otherwise would have limited or no access to asthma medication, there may [be] additional opportunities in the Asthma Learning Center with which to educate them more adequately about their disease."

Ms. Cohen also observes that the G3 Engineering Report does not characterize Primatene's anticipated user group as identical with the labeled indication. Its definitive conclusion on page 15 states that (b) (4)

However, Ms. Cohen questions whether (b) (4) s the same as "temporary relief of mild symptoms of intermittent asthma." She notes that the report's characterizations of the anticipated user group contain two other inconsistencies:

- Page 15 also states: "*failure to properly complete this sequence (of initial priming) may*

result in the user receiving a slightly higher or lower dose of medication for the first several sprays, which in turn could result in incomplete relief of their mild to moderate asthma symptoms."

- Page 18 states: "*the residual risks are outweighed by the benefits for patients using the device. These benefits include.....over the counter temporary relief of intermittent symptoms of mild asthma.*

In her review, Ms. Cohen writes, "these statements are somewhat contradictory in their definition about the anticipated user group, in that they varyingly refer to mild asthma users, mild to moderate asthma users, users with mild symptoms of intermittent asthma and users with intermittent symptoms of mild asthma." She defers to clinical reviewers "to determine whether this reflects merely a semantic inconsistency and therefore is not a concern, or whether this inconsistency could point to possibly a different benefit/risk calculation that FDA might make, based on the same bench data and human factors data."

Therefore, Ms. Cohen suggests that "FDA may want to consider asking the Applicant to conduct the actual use study that it had previously directed the Applicant to conduct. An actual use study could not only assess users' problems, if any, with the product, but it could also independently assess the severity of asthma symptoms of those who chose to purchase the product, which might be helpful in refining benefit/risk calculations." She notes that the Sponsor claims (b) (4)

However, Ms Cohen points out that, "while this is a valid point, I believe that the Applicant could advertise for sufferers of mild symptoms of intermittent asthma (in other words, the labeled indication for this product) and then assess whether the sufferers' definition of "mild" and "intermittent" is in fact aligned with the Applicant's definition of "mild", and "intermittent" by assessing actual patterns of usage and any difficulties with the use of the product."

Ms Cohen concludes that, "from a consumer perspective, since the labeling was significantly revised after LCS VI, the key research input for an approval decision is the human factors study." She recommends the following:

- The Sponsor should be asked to justify (b) (4)

- With regard to the summary page, the Sponsor should be asked to add (in consumer friendly language) that the (b) (4) indicator only moves after 20 actuations are completed.

- With regard to the Asthma Learning Center, clinical reviewers may want to weigh in on whether there needs to be additional presentation on asthma severity definition and treatment options. In any case, the (b) (4) section should be moved up front from its current placement at the back.

- Clinical reviewers should consider requesting an actual use trial if there are any continuing concerns about the ability of consumers to safely and effectively administer this product in a real life situation.

CDTL Comment: The three label comprehension studies in this Complete Response (LCS IV, V, and VI) are analyzed in further detail in the Biostatistics Review (summarized below). As described above by Ms. Cohen, the studies illustrate the difficulties of adequate comprehension for use by consumers, particularly those with low literacy and those with prior experience with use of Primatene. The latter group appears to assume that the new Primatene (HFA) works the same way as the old Primatene (CFC). However, I agree that, since the labeling was significantly revised after LCS VI, the key research input for an approval decision is the human factors study.

Ms. Cohen also raises an important point about possible contradictory definitions about the anticipated user group. From clinical standpoint, the product is intended for treatment of mild symptoms of intermittent asthma. It is not intended to be used on a regular basis for subjects who have mild, moderate, or severe persistent asthma. These patients require additional treatment and evaluation by a healthcare professional. Thus, labeling appropriately states to see a doctor if the user is not better in 20 minutes, gets worse, needs more than 8 inhalations in 24 hours, or has more than 2 asthma attacks in a week. The proposed DFL for epinephrine-HFA proposes an indication for "mild symptoms of intermittent asthma" which includes patients with intermittent asthma only. In addition, the label contains the statement, "do not use unless a doctor has said you have asthma." This indication and warning are consistent with the previously marketed epinephrine-CFC product.

Human Factors Study: DMEPA Review

A review of the Human Factors Study was conducted by Grace P. Jones, PharmD, BCPS, Division of Medication Error Prevention and Analysis (DMEPA). The review included evaluation from a medication error perspective of the human factors (HF) validation study report, the proposed instructions for use (IFU) for Primatene Mist, and the container and carton labeling. DMEPA analysis of the findings from the HF validation studies informed DMEPA review of the proposed IFU, container label, and carton labeling.

Ms Jones' review and recommendations are discussed in detail below. As stated in her review, DMEPA concluded that, "the HF validation study was unable to demonstrate that the intended user population is able to use the product safely and effectively. The failures noted in the HF study would result in patients receiving either an overdose or an underdose potentially resulting in lack of efficacy. Thus, we provide labeling recommendations….. for the applicant to implement corrective and preventative measures to improve the product-user interface that may decrease this risk. However, in light of our post-marketing experience with similar prescription HFA MDIs, we anticipate that these changes are unlikely to eliminate the risks altogether."

The Sponsor submitted the proprietary name [redacted] (b) (4) for review on 30 June 2016; however, DMEPA held a teleconference with the Sponsor to discuss concerns surrounding the proposed proprietary name and alternative naming options. On 19 September 2016, the Sponsor submitted the proposed proprietary name, Primatene Mist, for review which DMEPA

found acceptable.

The Sponsor submitted the following HF validation study reports:

- A statistical Quantitative Analysis HF Report
- A HF Engineering Report

The HF Engineering Report provided qualitative data from the HF validation study. The DMEPA review primarily focused on the qualitative data provided in the HF Engineering Report. Analysis of the statistical data was deferred to Biostatistics.

The HF validation study was a combination simulated-use, behavioral, and label comprehension study designed to evaluate 6 tasks based on the usability of the proposed inhaler device and the proposed accompanying IFU. The first 3 tasks were comprised of simulated-use tasks, which were the primary endpoints:

1. Initial priming,
2. Cleaning and prevent clogging,
3. Routine use of the inhaler device.

Participants' performance scoring for the behavioral simulate-use tasks were coded as follows:

- **Completed (C)**: Participants successfully performed the use task and demonstrated an understanding of the communication objective
- **Completed with Issues (CI)**: participants successfully performed the use task and demonstrated understanding of the communication objective but either struggled initially to do so, self-corrected during the testing session, or completed the task in such a way that differs from the IFU and after being referred to the instructions by the study moderator, successfully performed the task and demonstrated understanding
- **Not Completed (NC)**: participants did not complete the task successfully or demonstrate understanding of the communication objective.

The remaining 3 tasks were comprised of labeling comprehension questions, which were the secondary endpoints:

4. How to interpret dose indicator,
5. Not relying on dose indicator if dropped,
6. Understanding correct finger positioning to ensure the device expels medication properly with each spray.

Participants' performance scoring for the labeling comprehension questions were coded as follows:

- **Correct (C)**: participants independently and without prompting articulated a correct understanding of the communication objective and described a correct strategy for achieving that objective
- **Not Correct (NC)**: participants did not articulate a correct understanding of the communication objective or describe a correct strategy for achieving that objective.

In her review, Ms Jones reported that DMEPA identified the following deficiencies associated with the study design:

- The study was conducted with only 15.9% of participants who were low literate (24 of 151 participants), which appears to be a disproportionate representation of adults in the United States with low literacy skills. However, Ms Jones wrote, "since we typically expect a minimum of 15 users in each distinct user group, we found that the applicant included sufficient quantity of low literate participants for evaluation of the study results."
- Performance scoring for the simulated use behavioral tasks were reported as completed (C), completed with issues (CI), or not completed (NC). The Sponsor considered scores of C and CI to be a successful completion of the simulated use task. However, Ms. Jones wrote, "we disagree that CI scores represent successful completion of the task since participants in the CI scoring category were prompted to refer to the instructions or the information on the carton at any time during the behavioral tasks, and study moderators could refer participants to the instructions to allow for an error to be self-corrected." She continued, "these deviations of prompting and self-correcting are not reflective of the real life OTC use environment. Additionally, in real life OTC use environment, the expectation is that users can use the product and the IFU safely and effectively without assistance. Thus, we evaluated all scores of NC and CI as use related errors in our analysis of the HF study results."

The HF study was conducted in 151 participants whereby each performed the 3 simulated use tasks and then responded to open-ended questions that assessed the participants' understanding of the 3 remaining label comprehension tasks. A brief summary of the study results are as follows:

Initial Priming Errors (Task 1):

For the initial priming task, there were 46 use errors reported, including 8 participants with scores of NC and 38 participants with scores of CI, as shown in **Table 7** below (electronically copied and reproduced from Ms Jones' review):

Table 7: Initial priming of the inhaler – Distribution of use error by user group

	Not Completed (NC) n=8				**Completed with Issues (CI) n=38**			
	Normal Literacy		**Low Literacy**		**Normal Literacy**		**Low Literacy**	
Inhaler Experienced	***Naïve***	***Yes***	***Naïve***	***Yes***	***Naïve***	***Yes***	***Naïve***	***Yes***
Adult	1	2	2	2	23	4	5	2
Juvenile		1			2	2		

All 46 participants failed to correctly perform the "shake and spray" subtask in the overall initial priming task. To complete this task, the IFU instructs the user to shake the inhaler, then spray the inhaler into the air, and repeat this sequence 4 times. However, 22 participants shook the inhaler once and then sprayed 4 times sequentially (scored by Sponsor as CI); 6 participants shook the

inhaler once and then sprayed fewer than 4 times sequentially (scored as CI); 4 participants shook the inhaler and sprayed twice, then shook the inhaler again ,and then sprayed 2 more times (scored as CI); 4 participants **did not shake** the inhaler or spray into the air prior to taking an inhalation (scored as NC); 3 participants **did not shake** the inhaler, but sprayed into the air 3 or less times (scored as CI); 2 participants **did not shake** the inhaler or spray it into the air before using, thus making no attempt to first prime (scored as CI); 2 participants **did not shake** the inhaler but sprayed into the air 1 or more times (scored as NC); 2 participants removed the container to shake it (scored as NC); and 1 participant shook the inhaler once and then sprayed 4 times sequentially but took longer than 10 seconds to complete the sequence (scored as NC).

Ms. Jones notes that, in parallel with the formative HF study, the Sponsor conducted bench studies to further evaluate the effect and potential risk of priming (see also **Section 1 Product Quality**). The initial priming bench study results showed that if the initial priming is performed by 1 shake followed by 4 or 5 consecutive sprays as long as the duration of the priming sequence does not exceed 10 seconds, then there would be minimal risk of diminished safety and effectiveness of the proposed inhaler device. The Sponsor also notes that if the initial priming use error occurs in the real OTC use environment, whereby the inhaler is not primed for first use, then the first 3 or 4 inhalations would essentially serve to prime the inhaler.

Of the 46 errors described above, there were 35 participants who did not follow the initial priming sequence as described in the IFU but shook the inhaler at least one time, which allows for the epinephrine aerosol suspension to become uniform. Twenty-six (26) of these participants met the criteria of the bench study, performed the priming in an acceptable sequence, or self-corrected independently during the simulated use task and received scores of CI.

However, eleven (11) participants **did not shake** the inhaler during the initial priming task. Six (6) of these participants received scores of CI indicating they did not shake the inhaler during the initial priming task but later self-corrected. Thus, Ms. Jones opines that it is feasible that these participants were referred to the instructions during the simulation. The Sponsor indicated that not shaking the inhaler can affect drug content uniformity of the proposed inhaler device. **Table 8** below (electronically copied and reproduced from Ms Jones' review) provides details of the participants who did not shake the inhaler in the initial priming task based on user groups. Ms. Jones notes that only 2 of these 11 participants were previous users of the formerly marketed CFC Primatene Mist product.

Table 8: Subtask not shaing the inhaler in the initial priming task - Distribution by user group

	No Shaking n=11 (Not Completed (NC) n=5 and Completed with Issues (CI) n=6)			
	Normal Literacy		**Low Literacy**	
Inhaler Experienced	***Naïve***	***Yes***	***Naïve***	***Yes***
Adult	4	1	1	4
Juvenile		1		

The provided root cause analysis for the use errors included the following: failure to read or refer to the IFU prior to completing the task, negative transfer based on prior inhaler experiences, confusion caused by the presentation of instructions in the IFU and the complexity of the repeating pattern of shake and spray 4 times, and one participant understood the instructions but chose not to comply. For example, participants referred to the picture in Step 4 in the IFU (Shake and Spray into the air) instead of reading the instructions, which led to misinterpretations of Step 4.

In summary, DMEPA's analysis of the study results determined that, after all acceptable mitigations including mitigations from the Sponsor's bench testing results were applied, 13% of participants (20 participants out of 151 total participants) failed this initial priming task.

Cleaning the Inhaler Errors (Task 2):

For the cleaning task, there were 60 use errors reported, including 4 participants with scores of NC and 56 participants with scores of CI. Successful completion of this task included removing the drug container, removing the cap, rinsing the inhaler mouthpiece for 15 seconds, and reassembling the inhaler. DMEPA notes that the instructions in the IFU indicate to wash both ends of the inhaler by running water through the mouthpiece for 30 seconds, however, the Sponsor conducted bench studies which demonstrated that a more liberal rinse time of at least 2 seconds is adequate to prevent the inhaler from clogging. Therefore, the instructions in the IFU of washing for 30 seconds are a more conservative approach and cleaning the mouthpiece for at least 15 seconds during the simulated-use task was considered acceptable.

Of the 56 participants who did not clean the inhaler according to the IFU but self-corrected during the simulated use task, 52 participants did not wash the inhaler for at least 15 seconds, and 12 participants did not remove the drug container. Note that participants were listed twice if they experienced both kinds of use errors (i.e., not washing the inhaler for at least 15 seconds and not removing the drug container). Therefore, the number of use errors equaled more than 56. Of the 4 participants with scores of NC who failed the task, 3 did not remove the container so that the mouthpiece could be washed nor did they demonstrate understanding that washing the inhaler prevents clogging, and 1 participant did not wash the mouthpiece despite demonstrating understanding of the need to wash the inhaler. The distribution of use errors based on the user groups is shown in **Table 9** below (electronically copied and reproduced from Ms .Jones' review).

Table 9: Cleanming the inhaler – Distribution of use errors by user group

	Not Completed (NC) n=4				**Completed with Issues (CI) n=56**			
	Normal Literacy		**Low Literacy**		**Normal Literacy**		**Low Literacy**	
Inhaler Experienced	***Naïve***	***Yes***	***Naïve***	***Yes***	***Naïve***	***Yes***	***Naïve***	***Yes***
Adult		1	1		37	5	6	1
Juvenile	1	1			2	5		

The provided root cause analysis for the use errors included the following: a lack of awareness of the need to clean the inhaler resulting from a failure to read the instructions for use prior to

completing the task and a negative knowledge transfer from prior inhaler experience and abnormal use. Additionally, there were 15 use errors in the twist and pull out container subtask, and 23 use errors in the wash either end, running water subtask.

In summary, DMEPA's analysis of the study results determined that, after all acceptable mitigations including from the Sponsor's bench testing results were applied, 12% of participants (18 participants out of 151 total participants) failed this initial priming task.

Routine Use of the Inhaler Errors (Task 3):

For the routine use task, there were 23 use errors reported, including 2 participants with scores of NC and 21 participants with scores of CI. This task required participants to re-prime the device by removing the cap, shaking and spraying once, with finger on center of the top of the inhaler container while not placing inhaler in the mouth, and then delivering an inhalation and replacing the cap. Two (2) participants did not re-prime the inhaler at all and failed the task (saw the instructions but chose not to re-prime), eight (8) participants initially failed the task but eventually self-corrected after being referred to the instructions, eight (8) saw the instructions but did not complete them as directed, one (1) did not read the IFU, and four (4) self-corrected independently. The distribution of use errors based on the user groups is shown in the **Table 10** below (electronically copied and reproduced from Ms Jones' review).

Table 10: Routine use of the inhaler – Distribution of use errors by user group

	Not Completed (NC) n=2				Completed with Issues (CI) n=21			
	Normal Literacy		Low Literacy		Normal Literacy		Low Literacy	
Inhaler Experienced	***Naïve***	***Yes***	***Naïve***	***Yes***	***Naïve***	***Yes***	***Naïve***	***Yes***
Adult				1	11	4	4	2
Juvenile	1							

The provided root cause analysis indicated that some use error participants did not read the IFU. Ms Jones observed that the use errors seen in the routine use of inhaler task are similar to the use error for task 1, initial priming.

In summary, DMEPA's analysis of the study results determined that, after all acceptable mitigations were applied, 13% of participants (19 out of 151 total participants) failed this initial priming task.

Interpreting the Dose Indicator (Comprehension Task 4);

There were 2 participants who did not recognize that the inhaler had a Dose Indicator, did not understand how it functioned, and did not notice the Red Zone indicator. The provided root cause analysis indicated that the participants did not realize the inhaler had a dose indicator either because they did not look at the IFU or because they did not appear to understand the word indicator. Of note, both participants were adult low literacy inhaler experienced participants.

Do not rely on the Dose Indicator if Dropped (Comprehension Task 5):

There were 4 participants who did not demonstrate comprehension of the instructions and did not articulate an appropriate approach for a dropped inhaler. The provided root cause analysis indicated that the participants did not realize the inhaler had a dose indicator, one participant in particular did not find the dose indicator during the test session, and the instructions on the IFU did not convey the risk of a malfunctioning Dose Indicator or the potential risk of running out of medication unexpectedly.

The Sponsor also conducted bench studies evaluating the risk of poor device performance and dose indicator functionality from accidentally dropping the inhaler. The study results showed that the risk of product malfunction is low (0.08%) if the inhaler is dropped from 5 feet to a concrete surface.

Correctly hold the inhaler (Comprehension Task 6):

All participants demonstrated comprehension of the correct finger position to hold the inhaler properly.

DMEPA Overall Assessment

DMEPA concluded that the HF study failed to demonstrate that the proposed HFA inhaler device can be safely and effectively used by the intended users. In her review, Ms. Jones wrote, "there were errors in the HF study particularly related to the simulated use tasks which can lead to medication error risks when the inhaler is used improperly, including overdose, underdose, or lack of efficacy." Furthermore, DMEPA's analysis of the HF study results determined that for the 3 simulated use tasks after all acceptable mitigations were applied, there were 20 failures for Task 1 Initial Priming (20/51, 13%), 18 failures for Task 2 Cleaning the Inhaler (18/151, 12%), and 19 failures for Task 3 Priming for Routine Use (19/151, 13%), which led to a total of 57 task failures (57/181, 38%). In addition, Ms. Jones wrote, "based on these results, we determined that there were 30% of participants (45/151) who failed at least one task."

Subsequently, DMEPA made the flowing determinations regarding the 3 simulated-use tasks (Tasks 1-3):

1) ***Not priming the inhaler device on first use or during routine use and not shaking the inhaler device may lead to overdose***.

   DMEPA Comment (Ms Jones' Review): "We acknowledge the Applicant's data supporting that the inhaler can be initially primed by shaking the inhaler once and spraying into the air 4 or 5 times all within 10 seconds. However, 11 participants did not shake the inhaler at all during the initial priming task, and during the routine use task, 2 participants did not re-prime the inhaler at all. There remains the residual risk that consumers may not initially prime and not shake the inhaler device for first use, and not re-prime for routine use. Based on our discussion with OPQ, we learned that since the proposed product is a suspension, shaking is a necessary action to allow the suspension to become uniform, and if an inhaler is not shaken and a consumer takes an inhalation (up to 3 inhalations), the doses received may be super potent. We considered the potential safety concern for a super potent dose and clinical significance of an overdose and based on our

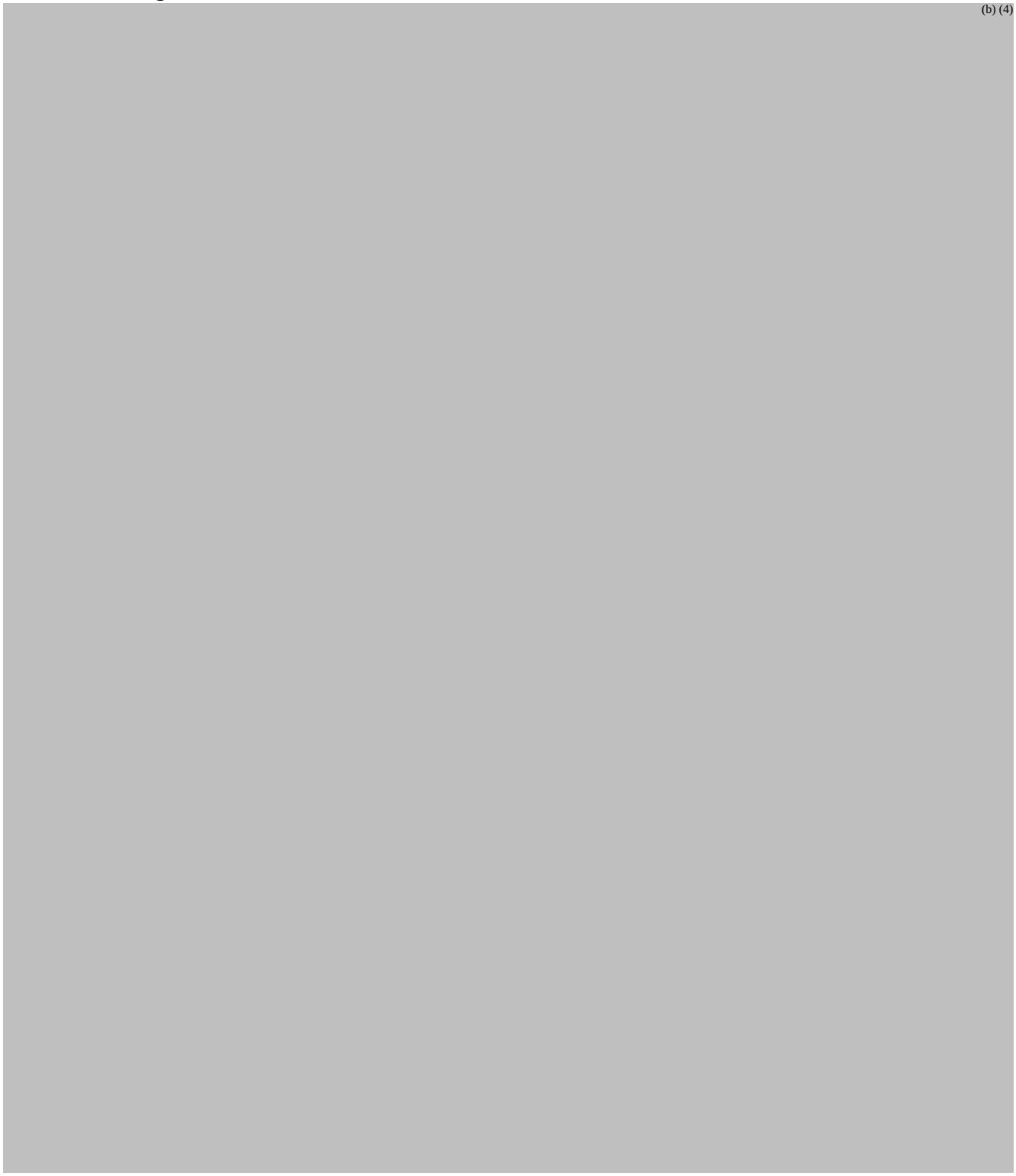
discussion with the Medical Officer, there may be limited clinical concern for an overdose because data from a safety study showed that high doses and the labeled warnings are acceptable from a cardiovascular effects perspective."

2) ***Not cleaning the inhaler device properly may lead to underdose or lack of efficacy.***
DMEPA Comment (Ms Jones' Review): "We acknowledge the Applicant's data supporting that the inhaler can be washed for at minimum 2 seconds versus the 30 seconds as indicated in the IFU. Despite this, there were 4 participants who washed the inhaler for less than 2 seconds. Thus, there is residual risk of consumers not cleaning the inhaler sufficiently which can lead to the delivery of reduced product or no drug product during use, constituting an underdose. Based on our discussion with OPQ, the continued use of a clogged inhaler would result in a suboptimal actuation and reduced potency of the drug product. In this event, consumers would receive an underdose, and may experience a lack of efficacy. However, based on further discussion with the Medical Officer, it may be expected that consumers would attempt to reuse the inhaler or seek medical attention if asthma symptoms are not relieved in 20 minutes, as instructed by the Drug Facts Label."

3) ***Not comprehending the Dose Indicator or what to do if the inhaler were dropped may lead to lack of efficacy.***
DMEPA Comment (Ms Jones' Review): "We acknowledge the Applicant's data supporting that the inhaler and the dose indicator would not malfunction if dropped. However, the concept of a dose indicator is new to the OTC marketplace and despite the Applicant's bench data, 2 participants could not interpret the dose indicator. If consumers do not comprehend the purpose of the dose indicator, they may continue to utilize the inhaler when in fact no more actuations remain, thus, consumers would experience a lack of efficacy. In terms of clinical significance to this risk, similar to not cleaning the inhaler device properly, we can anticipate if consumers' asthma symptoms are not relieved with the proposed product, based on the proposed product's labeling, consumers would seek medical attention."

In summary, DMEPA concluded that the HF validation study was unable to demonstrate that the intended user population is able to use the product safely and effectively. DMEPA provided labeling recommendations for the Sponsor to implement corrective and preventative measures to improve the product-user interface that may decrease the risk (see below). However, DMEPA also stated that "we are unable to conclude that any labeling mitigation would eliminate the potential for medication errors entirely. We are aware of post-marketing errors with prescription HFA MDI products with similar product-user interfaces, despite their use under a prescriber's supervision. The known use errors with prescription HFA MDIs include not shaking the inhaler before each dose and not properly cleaning the inhaler device. We note these known use errors are similar to those use errors observed in the proposed product HF study, thus we anticipate use errors for the proposed product to be similar to those observed with the prescription products, if approved." DMEPA continued, "we defer to the Review Division for determination of whether the benefits of introducing this epinephrine inhalation product with its proposed user interface outweighs the risk for use errors that can result in improper dosing."

DMEPA Labeling Recommendations:



Biostatistics Review

Statistical review and evaluation of the three label comprehension studies (LCS IV, V, and VI)

and the Human Factors Study (G3) was performed by Yueqin Zhao, PhD, Division of Biometrics IV. In her review, Dr Zhao summarized the studies performed and the study findings. In each LCS and comprehension objective, the Applicant assessed comprehension relative to the performance threshold of 85% for the general population. LCS IV focused on subject comprehension of instructions for washing, priming, re-priming and using the device. All the comprehension objectives were met in LCS IV except the one for "priming the inhaler when wet or not used for 2 days". Thus, the label was revised and this latter comprehension objective was tested again in LCS V. In addition, LCS V tested the objective for the prime before first use and place finger on center of dose indicator. The objectives for the prime before first use and place finger on center of dose indicator were met in LCS V, and the objectives of "for priming the inhaler when wet or not used for 2 days" were re-tested in LCS VI after label revisions.

Dr. Zhao determined that in LCS IV, LCS V and LCS VI, specific subject comprehension levels met the 85% threshold for the general population after the label was updated. The comprehension still fell below the 85% threshold in low literacy subjects for the following evaluation objectives:

1. Prime before first use;
2. Place fingers on center of dose indicator;
3. Do not use more than 8 inhalations in 24 hours;
4. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take;
5. Prime the inhaler if wet or not used for 2 days.

As described above, the human factor study was conducted in 151 subjects (>12 years old) from two sites. This study assessed consumers' ability to carry out tasks related to use and maintenance of the MDI: (i) First Use (initial priming), (ii) Cleaning to prevent clogging , and (ii) Routine Use. In addition, the study assessed understanding level of the labeling: (i) Dose Indicator, (ii) Dropped Device (not relying on the dose indicator if dropped) and (iii) Hold Inhaler Properly (understanding the correct finger position). Using the Sponsor's data, which included all participants who Completed with issues (CI) as successfully Completed (C), Dr. Zhao determined that subjects showed good comprehension for all the tasks related to priming, cleaning and routine use and all the label comprehension questions on dose indicator, dropped device and holding inhaler properly. However, subgroup analyses showed that subjects with the following characteristics did not perform as well in all tasks (i) a very short reading time of E004 IFU (instruction for use), (ii) low literacy level, and (iii) carryover habit of prior inhaler experience.

By using the original dataset and the Sponsor's's definition of acceptable rate, all acceptable rates and their lower limits of 95% exact CI were above 85% for all Critical Behavioral Tasks (CBTs) and Additional Labeling Human Factors Questions (ALHFQs). However, Dr. Zhao further noted that if only Complete (C) responses are considered acceptable, the acceptable rate for Task 1 First use was estimated as 70 % with 95% confidence intervals as (62%, 77%), the acceptable rate for Task 2 Cleaning was estimated as 60% with 95% confidence intervals as (52%, 68%) and the acceptable rate for Task 3 Routine use was estimated as 85% with 95% confidence intervals as (78%, 90%).

Dr. Zhao concluded, "the reviewer was able to reproduce the results provided by the Applicant."

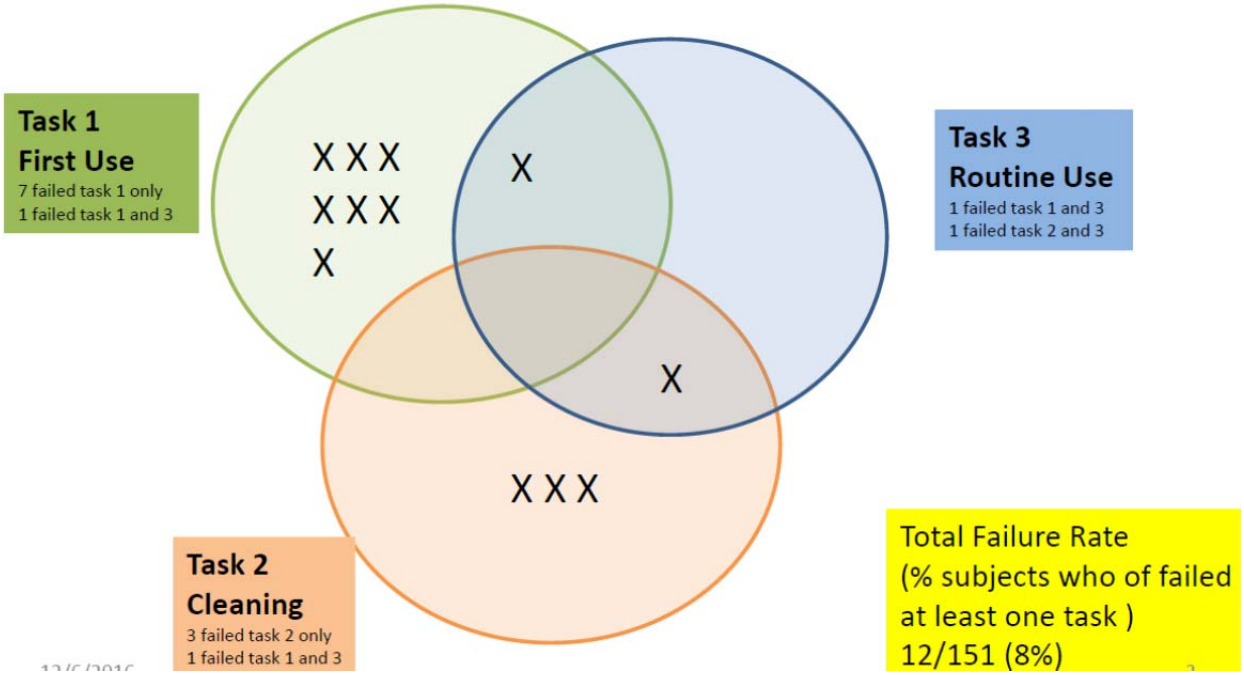
However, Dr. Zhao further noted that, "the comprehension objectives on 'Prime the inhaler again if it is wet' and 'Prime the inhaler again if not used in 2 days' were tested in all three label comprehension studies. The thresholds of 85% comprehension level for these objectives were not met in LCS IVand LCS V but were met in LCS VI. It is a challenging instruction for potential users to comprehend. However, during the revision of the PI or IFU for Human Factor study G3, no sufficient information on 'Prime the inhaler again if wet or not used in 2 days' was provided in the proposed Instruction For Use. Therefore, Dr. Zhao recommended "that additional instructions about priming should be included in the Instructions for Use (IFU)," and further concluded that "the instructions for use of 'Prime the inhaler again if it is wet or not used in 2 days' was difficult to understand relative to other tested messages in the label comprehension study. Comprehension rates for this instruction did not exceed 85% in LCS IV, LCS V but did exceed 85% in LCS VI. Although the PI and DFL were revised, the IFU was not revised. The reviewer believes that the additional instructions should be included in the IFU, so that potential consumers can safely use the product."

Additional Analysis: DMEPA and Biostatistics

Subsequent to Dr. Zhau's analyses above, the Biostatistics team re-worked the number of failures (NC and CI) based on DMEPA's determinations as to the number of failures after mitigations. The goal was to establish the number of subjects who were unable to correctly operate the drug product, that is, the percent of participants who failed at least one of the 3 primary, simuated-use tasks. The Biostatistics Team was able to confirm DMEPA's findings, as shown in the following diagrams (electronically copied and reproduced from Biostatistics email communication; Rima Izem, PhD).

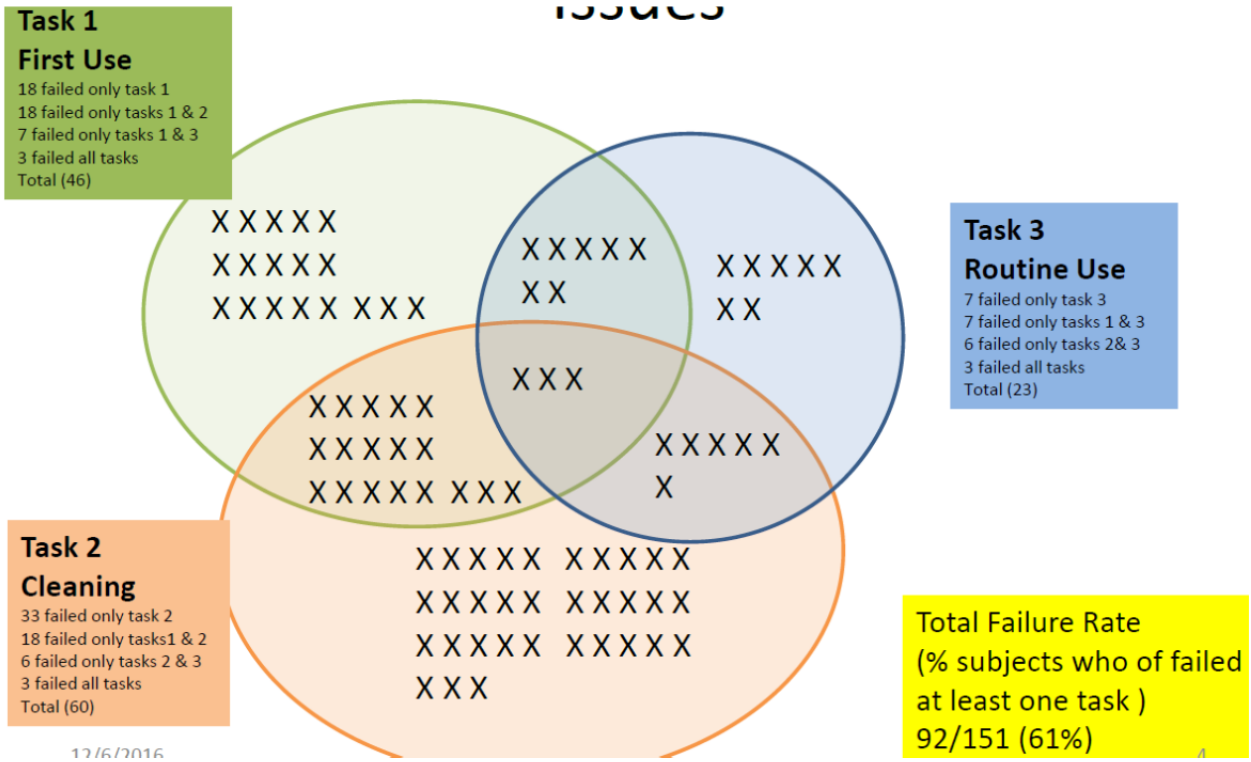
According to the Sponsor who, as noted above, considered all participants in the HF study who were classified as CI to be adequately mitigated and therefore not failures, the percentage of participants who failed at least one of the 3 primary tasks is shown in **Figure 8** below:

Figure 8: Failures in Primary Tasks (Human Factor's Study: Sponsor's Assessment)



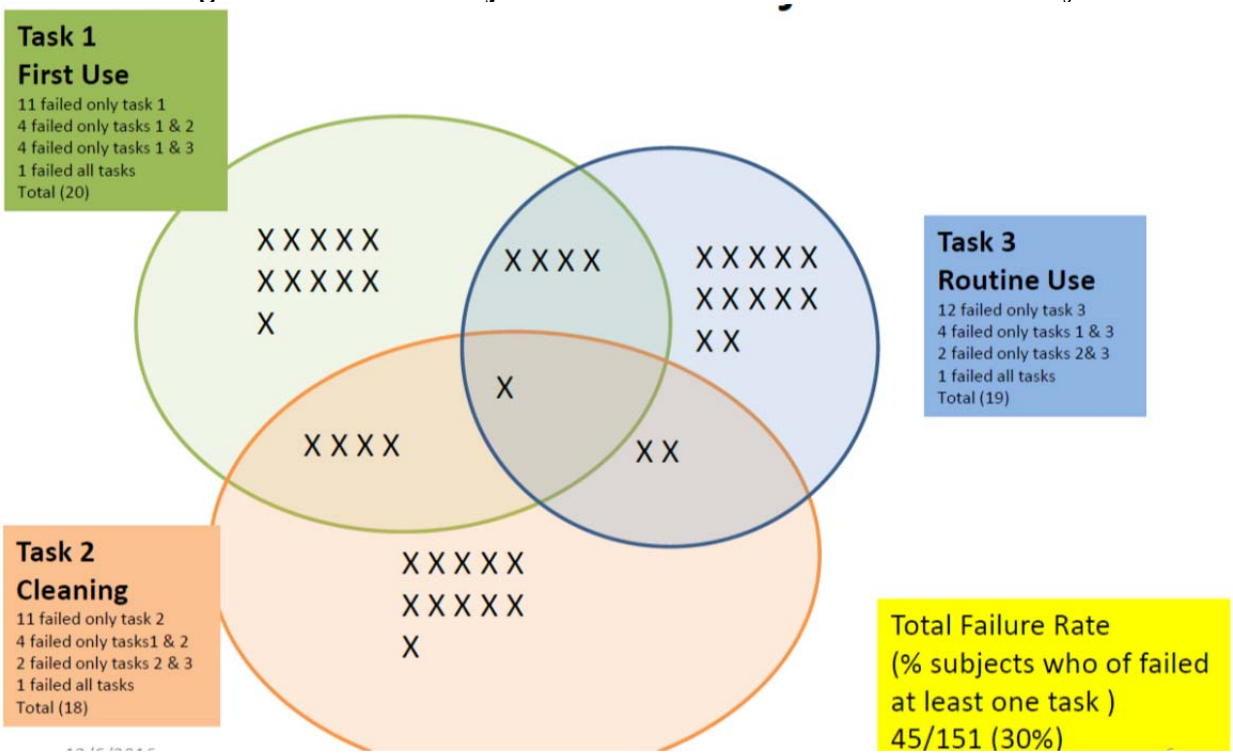
If all of the participants in the Human Factors Study who were classified as Complete with Issues and therefore included with those who were classified as Not Complete (NC) as failures, the diagram would be as follows:

Figure 9: Failures in Primary Tasks (Human Factor's Study: Failure = NC + CI)



However, based on DMEPA's review and adjudication,, the Diagram is as follows:

Figure 10: DMEPA Adjudicated Failures in Human Factors Study



The discrepant results of the Sponsor's analysis compared to DMEPA's analysis are summarized in **Table 11** below (electronically copied and reproduced from Biostatistics email communication; Rima Izem, PhD):

Table 11: Completion and Failure Rates – Human Factors Study

	Complete	Incomplete or Complete with Issues (DMEPA's failure rate)	Incomplete (sponsor's failure rate)	(NEW) Failure (DMEPA Adjudicated 12-2-16)
Task 1: First Use	105/151 (70%)	46/151 (30%)	8/151 (5%)	**20/151 (13%)**
Task 2: Cleaning	91/151 (60%)	60/151 (40%)	4/151 (3%)	**18/151 (12%)**
Task 3: Routine use	128/151 (85%)	23/151 (15%)	2/151 (1%)	**19/151 (13%)**

CDTL Comment: As noted by DMEPA and discussed above, there were 20 particpants who

failed to adequately perform Task 1 and 19 participants who failed to adequately perform Task 3. I have had several discussions with DMEPA regarding these findings. Regarding initial priming, the shaking sequence is necessary to evenly distribute the drug in suspension and thus prevent the user from receiving a super-potent dose. In contrast, the spraying sequence is necessary to fully load the drug product so that users don't receive a partial dose. In both cases (failure to adequately shake and failure to adequately spray), consumers who adequately perform Task 3 (re-prime, that is shake and spray once), would correct the dosing content. Per OPQ ,it is likely that more than 2 shake and spray sequences would be adequate.

Eleven (11) participants did not shake the inhaler at all during the initial priming task. However, these 11 participants did not fail Task 3, so presumably they would self-correct over time. Only 4 participants failed both Tasks 1 and 3 (and 1 participant failed all 3 tasks), and during the routine use Task (Task 3), two participants did not re-prime the inhaler at all.

Thus, there remains the residual risk that consumers may not initially prime and not shake the inhaler device for first use, and not re-prime for routine use. Per OPQ evaluaton, participants who do not adequately shake the product are primarily at risk for a supratherapeutic dose. As stated by Dr. Christodolou in his review, "Because the suspension inherently settles upon standing, shaking and spraying before taking a dose is a critical instruction." OPQ has calculated that consumers who do not adequately complete the initial priming sequence may receive a hyper-potent dose of (b) (4) % label claim. However, as noted in ***Section 11*** *above, several pharmacodynamic safety studies have demonstrated that drug levels at doses nearly 13-fold higher than proposed (125 mcg versus 1600 mcg in one trial) were not likely associated with significant safety issues. Therefore, we can conclude that consumers who fail to correctly prime and receive supratherapeutic doses of epinephrine aerosol will not be at risk.*

However, not cleaning the inhaler device properly (Task 2)may lead to underdose or lack of efficacy. If a consumer receives a sub-therapeutic dose, they are at risk that their asthma symptoms will not be relieved. OPQ reported that the dose content uniformity (DCU) remained acceptable after a minimum of a 2 second rinse and was not impacted by dose content or drying time. Thus, Dr. Christodolou noted that the current instruction for cleaning, "run water through (b) (4) the mouthpiece for 30 seconds (b) (4) air dry overnight," is a conservative instruction. However, there were 4 participants who washed the inhaler for less than 2 seconds. Other participants who failed Task 2 did not remove the canister prior to cleaning. There remains a risk of under-dosing for these participants.

In summary, although 30% of participants in the HF study failed at least 1 of the 3 tasks, it is possible that some of these participants, particularly those who only failed Task 1, would correct dosing issues with continued use. If they receive a supra-therapeutic dose, there is no safety risk, and efficacy is acceptable. If dosing is sub-therapeutic , efficacy may be inadequate.

Labeling Review

At the time of this writing, Interdisciplinary Science (IDS) Labeling Team Review is ongoing, and labeling negotiations with the sponsor have been initiated. On 11 November 2016, an Information Request (IR) was sent to the Sponsor with requested revisions to the proposed PDP

and DFL. Requested revisions to the proposed DFL are shown **Appendix I** below.

An important point conveyed to the Sponsor concerned use of the terms (b) (4) which would likely cause confusion among consumers. To ensure, accuracy of information, FDA recommended replacing (b) (4) with Spray Indicator," (b) (4) FDA also recommended the term (b) (4) be replaced with "inhalation."

In addition, the Sponsor was asked to justify why (b) (4)

In the Sponsor's response to the IR (email to Tinya Sensie on 12 December 2016), the Sponsor essentially agreed with FDA changes and upgraded the DFL accordingly. The Sponsor to remove the (b) (4) warning.

13. Postmarketing Recommendations

None.

14. Recommended Comments to the Applicant

My recommended Comment to the Sponsor are outlined below and assume agreement within the FDA with my recommendation for a Complete Response:

The studies you have submitted (three label comprehension studies [LCS] and one human factors [HF] study) raise concerns about whether or not consumers can use your product correctly. We have concluded that approximately 30% of participants in the Human Factors Study failed at least one of the three primary tasks of the study: failure to adequately complete initial priming, failure to adequately clean the device to prevent clogging, or failure to adequately re-prime the inhaler for continued routine use. If these tasks are not correctly performed, users of this product may not correctly administer the product and therefore may under-dose or receive a supra-therapeutic dose. Clinically, because of the wide safety margin, a supra-therapeutic dose is unlikely to be problematic. However, under-dosing may result in lack of efficacy. This is a significant clinical safety concern.

It is unlikely that labeling mitigation would eliminate medication errors entirely. Post-marketing errors with prescription HFA products with similar product-user interfaces, have been reported despite their use under a prescriber's supervision. These known use errors with prescription HFAs are similar to those observed in the HF study. Thus, it is anticipated that use errors for the proposed product will be similar to those observed with the prescription products, if approved. Furthermore, it is unclear whether consumers who select to use this product will be appropriate for the proposed indication, that is "mild symptoms of intermittent asthma" or whether consumers with more severe or persistent asthma will use this product, and it is unclear if consumers who use the product and do

not experience adequate relief of symptoms will appropriately follow the "see a doctor" warnings.

As previously advised in the Complete Response letter of 22 May 2014, conduct a randomized, actual use study with the revised labeling and proposed epinephrine HFA inhalation aerosol to rigorously quantify and evaluate complaints or problems associated with use of the product and characterize sources of user error. We acknowledge your concern that it would be difficult to field such a study because mild sufferers only have occasional episodes; therefore, most episodes involving Primatene use would probably be beyond the timeline scope of a study. However, we do not agree and advise that, in an AUT, you advertise for sufferers of mild symptoms of intermittent asthma (in other words, the labeled indication for this product) and then assess whether the sufferers' definition of "mild" and "intermittent" is in fact aligned with your definition of "mild", and "intermittent" by assessing actual patterns of usage and any difficulties with the use of the product. Thus, an actual use study could not only assess users' problems with the product, but it could also independently assess the severity of asthma symptoms of those who chose to purchase the product, which might be helpful in refining benefit/risk calculation.

3 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 and this page is the manifestation of the electronic signature.

/s/

FRANCIS E BECKER
12/09/2016