CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205920Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)(2); SDN – 73 Class 2 Resubmission Second Resubmission – Response to Complete Response Letter
Application Number(s)	205920
Priority or Standard	Standard
Submit Date(s)	May 5, 2018
Received Date(s)	May 7, 2018
PDUFA Goal Date	November 7, 2018
Division/Office	Division of Nonprescription Drug Products (DNDP)/ODE IV
Reviewer Name(s)	Suhail Kasim, MD MPH
Review Completion Date	October 14, 2018
Established/Proper Name	Epinephrine Inhalation Aerosol
(Proposed) Trade Name	Primatene Mist
Applicant	Armstrong Pharmaceuticals, Inc.
Dosage Form(s)/ Route of Administration / Strength	Aerosol, metered / Inhalation (metered dose inhaler (MDI)/ 125 mcg per actuation
Applicant Proposed Dosing Regimen(s)	1-2 inhalations every 4 hours as needed maximum 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	Approval

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CIL	Consumer instructions for use Information Leaflet
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DFL	Drug Facts Label
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Armstrong Pharmaceuticals, Inc. (Armstrong) resubmitted the NDA 505(b)(2) supplement on May 7, 2018 for the third cycle review (second resubmission) seeking approval for epinephrine inhalation aerosol, using hydrofluoroalkane propellant in the single-ingredient drug-device combination metered dose inhaler product (hereafter referred to as epinephrine HFA) at a dose of 125 mcg per actuation for nonprescription use for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older.

During the epinephrine HFA development program, the product was referred to as E004. Primatene Mist is the proposed proprietary trade name.

A chlorofluorocarbon based Primatene Mist epinephrine metered dose inhaler (hereafter referred to as epinephrine CFC) was previously marketed, although it was withdrawn from distribution in 2011 when metered dose inhalers using ozone-depleting chlorofluorocarbon (CFC) propellants began to be phased out in 1996 in compliance with the Montreal Protocol. The epinephrine CFC metered dose inhaler was approved for nonprescription use for the treatment of symptoms of asthma on November 8, 1967 under NDA 016126. The previously marketed Primatene Mist epinephrine CFC metered dose inhaler was not discontinued due to reasons of safety.

This NDA 205920 supplement class 2 resubmission included Armstrong's complete response to deficiencies identified during the second cycle review and outlined in the letter dated December 23, 2016. An overview of the complete response and relevant discussions supporting the recommendations in the benefit-risk discussion for the epinephrine HFA nonprescription product are included in section 8.1 as they pertained to minimizing clinically important use errors that could result in superpotent dose or overdosing and subpotent dosing. Since there were no clinical trial data submitted to this third cycle NDA 205920 resubmission, this document provides a brief update of regulatory activities since the second cycle complete response, recommendations for the proposed labeling with supporting information, and information about required postmarketing pediatric studies under PREA. Previously reviewed clinical information to determine safety and efficacy will not be repeated in this document, and will include references to the information previously reviewed. Numbering for this review follows the clinical template, but missing headers are purposeful and not relevant to this review.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Clinical efficacy trials reviewed during the first review cycle demonstrated bronchodilator efficacy of epinephrine HFA compared to placebo for the primary endpoint for the proposed 125 mcg per actuation, and the efficacy results were also comparable to those observed with epinephrine CFC product. Effectiveness, i.e., whether the efficacy of the epinephrine HFA product is generalizable to nonprescription product consumers in 'real world' use, was assessed in the previously conducted label comprehension studies of consumer behavior, and in the behavioral human factors study.

Previous NDA 205920 submissions reviewed to support epinephrine HFA marketing discussed the objectives for the development program for epinephrine HFA and that it was designed to focus only on elements that differed from the previously available epinephrine CFC product label, and did not focus on self-selection or safety questions related to the label that are commonly evaluated as part of a de novo nonprescription product development program. Please see discussion of summary product characteristic differences between the epinephrine CFC metered dose inhaler compared to the currently proposed epinephrine HFA product in section 2, and Table 1.

Considering the above-mentioned objectives, the Division of Nonprescription Drug Products considered information obtained from human factors validation studies to be reflective of epinephrine HFA product use in the nonprescription setting. Consumers rely on the labeled packaging instructions without the intervention of healthcare provider/learned intermediary. Human factors studies are part of an iterative design process that is driven by the complexity of the combination product and the nature of the safety considerations. The human factors study evaluates: (i) the ability of the user to perform critical tasks, and (ii) the ability of the user to understand the information in the packaging and labeling, such as product labels or instructions for use, that inform the user's actions and that are critical to the safe and effective use of the combination product[1]. Minimizing use errors to the lowest possible level is essential for safe and effective nonprescription product use.

Simulated consumer interaction in the human factors studies conducted by Armstrong identified situations when there were user errors and task failures/failure modes in following the nonprescription product labeled instructions that were evaluated in human factor study G3 during the June 28, 2016 (Class 2 resubmission) review cycle. These critical task user errors were considered clinically significant performance issues and the overall risk-benefit assessment did not support approval of epinephrine HFA for the temporary relief of mild

[1] The draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016) is available on the FDA guidance web page at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm484345.pdf

symptoms of intermittent asthma for nonprescription use. Additional information was needed to determine whether the consumers can use the epinephrine HFA product correctly using the labeled information without the intervention of a health care professional/learned intermediary. Specifically, the data reviewed in the human factors study G3 showed clinically important use errors in at least one of the three primary critical tasks (see section 3.1) and there remained clinical concerns when these critical use tasks were not correctly performed because asthmatics may not receive therapeutic dosing.

In support of the marketing application during the second resubmission on May 7, 2018 to NDA 205920, Armstrong submitted data from human factors validation study G4 using the current iteration of the product label to understand device use. Information was reviewed to determine the adequacy of the human factors study G4 and whether the user interface was improved to support nonprescription use of epinephrine HFA for the temporary relief of mild symptoms of intermittent asthma. Additional supportive CMC bench study data was submitted that supported revisions of the directions for use and making the collective tasks less cumbersome.

Based on the available information reviewed in NDA 205920, Armstrong's application adequately demonstrated that consumers can use the drug-device product safely and properly without the intervention of a health care professional using the labeled information for nonprescription use to achieve the intended effect, i.e., for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. Information reviewed in the previous review cycles for the device and dose indicator showed reliable performance over the lifespan of the product.

1.3. Benefit-Risk Assessment

Please see Jenny Kelty, MD cross discipline team lead review for NDA 205920 benefit-risk integrated assessment summary.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☒	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

Please see Ryan Raffaelli, MD medical officer's clinical review of April 15, 2014 (DARRTS Reference ID: 3489745) for discussion of asthma including the discussion on the diagnostic category of interest, mild intermittent asthma; and for information on products like epinephrine available for managing acute asthma symptoms and other marketed short acting beta agonists.

To discuss briefly, patients diagnosed by their healthcare provider with mild, intermittent asthma, which is generally defined as experiencing symptoms on two or fewer days per week, use of a short-acting beta agonist for symptom control on two or fewer days per week, nighttime awakenings two or fewer times per month, have no interference of normal activities by asthma symptoms, have normal baseline lung function, and experience one or fewer exacerbations per year, are targeted for nonprescription epinephrine HFA metered dose inhaler use. The proposed indication statement in the drug facts label (DFL) for the epinephrine HFA product for nonprescription use is "for temporary relief of mild symptoms of intermittent asthma." 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. Patients with more frequent or persistent symptoms should be under a physician's care and the proposed DFL includes consumer warnings to "see a doctor".

As noted above in section 1.1, epinephrine CFC metered dose inhaler was available until 2011 and marketed for nonprescription use as Primatene Mist for almost 50 years without significant safety findings. The epinephrine HFA development program focused on elements that differed from the epinephrine CFC product label.

Most importantly, because of the differences in the propellant characteristics, the epinephrine HFA suspension formulation settles easily, and therefore the inhaler must be shaken vigorously and reprimed before each use to provide consistent therapeutic dosing. If the epinephrine HFA metered dose inhaler is not shaken, this could potentially result in dose variability leading to higher doses administered. The epinephrine HFA propellant requires cleaning due to the stickiness of HFAs to prevent product occlusion. Table 1 summarizes product characteristic differences between the epinephrine CFC metered dose inhaler Primatene Mist[2] compared to the currently proposed epinephrine HFA product.

[2] See archived drug label DailyMed and summary information in Armstrong submission dated June 28, 2016 (https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=13423)

Table 1: Comparison of Epinephrine Chlorofluorocarbon MDI and Epinephrine Hydrofluoroalkane MDI

	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	(b) (4) mouthpiece after each use	(b) (4)
Population	Ages 4 years and above	Proposed 12 years and above
Dosing regimen	1-2 inhalations every 3 hours; (b) (4)	1-2 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	**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

	• use more than 9 inhalations a day for more than 3 days a week • have more than 2 asthma attacks in a week	• 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 (b) (4) Wait 1 minute. If symptoms not relieved, take a second inhalation by repeating (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		

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.

Each epinephrine HFA metered dose inhaler contains 160 metered sprays 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 of eight inhalations per 24 hour period. The product is a standard press-and-breathe metered dose inhaler that comes assembled.

The epinephrine HFA metered dose inhaler includes a top mounted dose actuation indicator. This device attaches to the end of the drug product canister using an adhesive label. The dose indicator mechanically counts each actuation. The display advances every 10 actuations and is

labeled numerically in increments of 20. When 20 or fewer actuations remain, the display begins to turn red in color. The red zone continues to fill the display until the counter indexes to zero. At this point the display is at the zero count and completely red, indicating the need to replace the inhaler. After the zero count has been reached, additional actuations of the metered dose inhaler no longer advance the display.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Please refer to prior NDA 205920 reviews of Theresa M. Michele, MD (May 22, 2014; DARRTS Reference ID: 3511415) and Ryan Raffaelli, MD (April 15, 2014; DARRTS Reference ID: 3489745) for the relevant regulatory history for epinephrine HFA metered dose inhaler. Information abstracted from the above-mentioned reviews with updated interim submission related regulatory activities is included in section 3.2 of this review.

When the metered dose inhalers using ozone-depleting CFC propellants were phased out beginning in 1996 in compliance with the Montreal Protocol, the previously marketed epinephrine CFC metered dose inhaler was withdrawn from distribution in 2011. Armstrong began communications with FDA for reformulating epinephrine without CFCs during pre-IND meeting in 2007 (IND 74,286).

An initial submission to NDA 205496 for the epinephrine HFA based inhalation aerosol was received on April 8, 2013. This first submission to NDA 205496 was refused to filed because of inadequate electronic document formatting permitting substantive review as per 21 CFR 314.101(d).

Armstrong submitted information to NDA 205920 for their reformulated epinephrine HFA metered dose inhaler product with the new propellant (instead of CFC) on July 20, 2013. NDA 205920 received a complete response letter on May 22, 2014 during that first cycle review. In the first cycle, Armstrong conducted four consumer studies, including three label comprehension studies and one behavioral human factors study evaluating whether subjects could correctly use the device using the labeled information.

FDA took a complete response action on May 22, 2014 due to product quality, nonclinical, and clinical deficiencies, with the following deficiencies outlined:

- cGMP deficiencies for the active pharmaceutical ingredient
- lack of nonclinical data supporting safety of excipient thymol for chronic use via oral inhalation

- lack of assurance that consumers can adequately use the product correctly without the intervention of a health care professional

NDA 205920 was also the subject of a joint meeting of the Nonprescription Drugs Advisory Committee (NDAC) and the Pulmonary-Allergy Drugs Advisory Committee (PADAC) on February 25, 2014 as the epinephrine HFA product represented the only metered dose inhaler product available for nonprescription use.

Armstrong resubmitted the application for review on June 28, 2016 (Class 2 resubmission). Following review, DNDP communicated that although Armstrong made significant improvements to the user interface, Armstrong still needed to demonstrate that consumers could use the epinephrine HFA metered dose inhaler drug-device product for the intended use in the nonprescription setting (as labeled) without the intervention of a health care professional/learned intermediary for temporary relief of symptoms of mild, intermittent asthma. FDA took a complete response action on December 23, 2016.

Specifically, data reviewed in the human factors study G3 showed clinically important use errors with at least one of the three primary tasks (critical use tasks).

- (Task 1) initial priming (4shake+4spray) of the inhaler
- (Task 2) cleaning/washing of the inhaler
- (Task 3) routine use re-priming of the inhaler (1shake+1spray, and inhale)

DNDP analysis for the three primary tasks identified up to 13% of participants with errors in each of these tasks that could lead to clinically important subpotent or superpotent dosing. Because some participants had clinically important errors in more than one task, this yielded 30% of participants with an error for at least one task. It was of clinical concern if these tasks were not correctly performed because users of the epinephrine HFA nonprescription product for temporary relief of asthma symptoms would not reliably receive the correct dose. In the case of subpotent dosing, which will likely result in lack of efficacy with inadequate relief of asthma symptoms, may also result in worsening of asthma symptoms.

To resolve this second cycle review deficiency (second complete response letter issued December 23, 2016), Armstrong was recommended to conduct a human factors validation study, after re-evaluating the primary task failures and their associated root causes. DNDP recommended assessing consumer understanding and ability to complete the three primary use tasks (critical tasks) with the epinephrine HFA inhalation aerosol for: (1) initial priming of the inhaler, (2) cleaning/washing of the inhaler to prevent clogging, and (3) routine use (repriming) of the inhaler. Armstrong needed to further optimize labeling with information from the supportive human factors study demonstrating that consumers can appropriately use the device with the revised labeling. In addition to the DNDP recommended changes that were already adopted in the DFL, the consumer instructions for use, and the outer carton, further

changes were recommended for the device labeling regarding the mouthpiece instructions to make the instructions for use present on the orange-colored actuator both visible and consistent with the consumer instructions for use by adding pictograms for the key steps for safe and effective use.

Armstrong filed a formal dispute resolution request (FDRR) on June 27, 2017 to appeal the second complete response letter deficiencies (December 23, 2016), and requested that the data from the previously conducted human factors study G3 be considered adequate to support approval of epinephrine HFA. Additional CMC bench studies data were submitted during the FDRR. Armstrong's FDRR appeal was denied on September 1, 2017 and in the denial letter FDA indicated that additional CMC information (from studies that evaluated user errors) will be reviewed during the next NDA resubmission.

See section 8.1 for review of the response to FDA's December 23, 2016 complete response action letter.

3.2. Summary of Presubmission/Submission Regulatory Activity

Information included in this section is abstracted from NDA 205920 reviews of Theresa M. Michele, MD (May 22, 2014; and December 23, 2016 DARRTS Reference ID: 4033296) and Ryan Raffaelli, MD (April 15, 2014; DARRTS Reference ID: 3489745) with updated interim submission related regulatory activities.

IND 74286

March 27, 2007 pre-IND meeting

- Discussion of proposed epinephrine HFA MDI development program, including requirements for clinical efficacy and safety, consumer behavior studies, and data to support the reliability and robustness of the device and dose counter.

November 25, 2008 Communication

- Feedback provided on clinical trial design

October 26, 2009 IND submitted

- Feedback provided on proposed development program, including the need for detailed monitoring of cardiovascular vital signs, pharmacokinetic sampling, long-term safety data, consumer studies, and data to support the chemistry, manufacturing, and controls of the product.

October 29, 2010 EOP2 Meeting

- Dose-ranging did not appear to be adequate; exposure of 125 mcg dose higher than reference product; recommendation to explore doses lower than 125 mcg
- Recommendation for larger and longer pediatric clinical trial
- Include reference product in phase 3 trials

- Assess device performance, including ruggedness and reliability

May 10, 2011 Communication

- Based on preliminary results of the dose ranging trials, FDA recommended carrying forward the epinephrine HFA 125 mcg dose into the phase 3 program, noting that the systemic exposure from 125 mcg is higher than that with epinephrine CFC 220 mcg, a difference that will have to be supported by phase 3 data and addressed in the NDA

September 23, 2011 preNDA meeting

- Reiteration of the need for a minimum of 6 months of safety data
- A large (n~300) label comprehension/behavioral use trial is required
- Concerns raised regarding the product's potential need for once-daily cleaning
- FDA requested device performance data under different in-use conditions to assess the impact of not cleaning the mouthpiece as directed
- Reminder to assess potential malfunctioning of the device with real-life usage
- Recommendation that the Sponsor request a second pre-NDA meeting upon the completion of phase 3

January 26, 2012 Communication

- Feedback provided on proposed long-term safety trial
- Requested safety data from at least 300 patients exposed for 6 months, which could be generated from already ongoing trials or from a new separate long term safety trial
- Requested pharmacodynamic data (i.e., blood pressure, heart rate)
- Deferred discussions of the pediatric program until efficacy and safety data in adults and adolescents were available

April 23, 2012 Communication

- Feedback provided on proposed label comprehension study

January 31, 2013 2nd preNDA meeting

- Recommendations on submission of specific pharmacodynamic data, AEs, serial FEV1 data and literature review in NDA submission
- Recommendation that NDA submission include evaluations of device performance during real-life use, evidence of device ruggedness, and a discussion of the potential for device clogging as well as justification for device cleaning instructions
- Concerns raised regarding adequacy of data in pediatric patients 4 to 11 years of age. Armstrong stated they may submit the NDA for adults 18 years of age and older. FDA raised concern that the epinephrine CFC Primatene Mist product was labeled down to 4 years of age and consumers may use an epinephrine HFA product in patients down to 4 years of age. FDA advised the sponsor to submit all pediatric data with the NDA application, even if the age range proposed for approval is limited to adults.

<u>NDA 205496</u>

April 8, 2013 NDA 205496 submitted for epinephrine HFA (refuse to file)

- The application had several deficiencies that precluded substantive review (refuse to file

letter issued July 7, 2013)

NDA 205920

July 22, 2013 (initial NDA review)

- NDA 205920 resubmitted for epinephrine HFA and accepted for filing
- A new NDA number (NDA 205920) was provided because of the vast technical problems associated with the original NDA (205496) submission.

October 1, 2014 End of Review Type A meeting

- Discussion of proposed qualification program for the excipient thymol
- Recommendation to submit the results of the label comprehension and human factors studies for review and request a meeting to discuss study findings and the need for an actual use trial

May 22, 2014 Complete Response action

- product quality, nonclinical, and clinical deficiencies identified:
- cGMP deficiencies for the active pharmaceutical ingredient
- lack of nonclinical data supporting safety of excipient thymol for chronic use via oral inhalation
- lack of assurance that consumers can adequately use the product correctly without the intervention of a health care professional

January 22, 2016 FDA advice letter

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

June 28, 2016 Class 2 resubmission (second cycle NDA review)

- Human factors study (G3)
- User interface improvements
- CMC bench study data

December 23, 2016 Complete Response action

- Human factors study G3 failed to demonstrate that the user interface supports safe and effective use of the product by intended users for the proposed uses in the nonprescription setting.
- Human factors study G3 had approximately 30% of participants who failed at least one of the three primary tasks (critical use tasks) of the study: initial priming of the inhaler (Task 1), cleaning of the inhaler (Task 2), or routine use (re-priming) of the inhaler (Task 3). Because some participants had clinically important errors in more than one task, this yielded 30% of participants with an error for at least one task

September 2, 2017 Formal Dispute Resolution Request

- Appeal denied

March 2, 2018 FDA advice letter

- Feedback provided for human factors study G4 protocol design

May 7, 2018 Class 2 resubmission (third cycle NDA review)

- complete response to deficiencies identified during the second cycle in the letter dated December 23, 2016, the formal dispute resolution request appeal denied letter dated September 2, 2017, and the general advice letter dated March 2, 2017

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

To resolve deficiencies outlined in the second complete response letter issued December 23, 2016, Armstrong was recommended to conduct a human factors validation study, after re-evaluating the three primary use tasks (critical tasks) and their associated root causes, including an assessment of consumer understanding and ability to complete the primary use tasks with the epinephrine HFA inhalation aerosol.

Grace P. Jones, PharmD, BCPS, Division of Medication Error Prevention and Analysis (DMEPA) reviewed the human factors validation study report G4 and Muthukumar Ramaswamy, PhD, reviewed additional CMC bench data for the drug product provided to support directions for use and product labeling. Additional information supporting NDA 205920 and any applicable review discipline summaries may be obtained from prior NDA 205920 clinical reviews of Francis E Becker, MD (December 09, 2016; DARRTS Reference ID: 4025825) and Ryan Raffaelli, MD (April 15, 2014; DARRTS Reference ID: 3489745).

5. Sources of Clinical Data and Review Strategy

There was no clinical trial data submitted to resolve deficiencies outlined in the second complete response letter issued December 23, 2016.

Please refer to prior NDA 205920 clinical reviews of Theresa M. Michele, MD (May 22, 2014; DARRTS Reference ID: 3511415), Ryan Raffaelli, MD (April 15, 2014; DARRTS Reference ID: 3489745), and Francis E Becker, MD (December 09, 2016; DARRTS Reference ID: 4025825) for discussions of the clinical efficacy and safety data supporting marketing application for epinephrine HFA metered dose inhaler. Armstrong submitted materials for review of their complete response letter to the December 23, 2016 letter via eCTD submission \\CDSESUB1\evsprod\NDA205920\0071

Information regarding the product, and any relevant safety and efficacy information from the

above-mentioned reviews are abstracted and included where applicable for discussion, and to provide additional clinical context to the DMEPA and Drug Product quality assessment reviewers' recommendations to support directions for use and product labeling.

6. Review of Relevant Individual Trials Used to Support Efficacy

There was no clinical trial data submitted in the May 7, 2018 NDA class 2 resubmission.

7. Integrated Review of Effectiveness

See section 1.2.

8. Review of Safety

8.1. Integrated Assessment of Safety

There was no new clinical trial data submitted for the assessment of safety in the May 7, 2018 NDA class 2 resubmission.

Previously reviewed safety data for epinephrine HFA from the adult phase 3 clinical trial data that included a review of the cardiac safety of epinephrine HFA in addition to postmarketing reports of adverse events with epinephrine CFC did not identify serious safety signals, and the reviewed safety data was considered acceptable for approval. Considering the known pharmacologic and physiologic effects of epinephrine, and the higher systemic exposure for the proposed epinephrine HFA product dose of 125 mcg per actuation (4.5 times increase in C_{max}) when compared to the previously marketed epinephrine CFC Primatene Mist product dose of 220 mcg per actuation, several pharmacodynamic safety measures indicated that resultant drug levels at doses nearly 13-fold higher with epinephrine HFA product (125 mcg per actuation versus 1600 mcg in a high dose PK study in healthy volunteers) were not likely associated with significant safety issues. The high dose PK study in healthy volunteers demonstrated substantial increases in blood pressure (>50 mmHg systolic) and pulse (>60 bpm) in some patients 10 minutes after a single dose of 1250 mcg and 1600 mcg, although the median increases were more modest (pulse increase of 5-6 beats, systolic blood pressure increase of 9-14 mmHg, diastolic blood pressure increase of 1-3 mmHg). To achieve a dose of 1250 mcg, ten

inhalations of the proposed 125 mcg dose in rapid succession should be administered; a dose of 1600 mcg would require 12-13 inhalations. Importantly, there was no data identifying a cardiovascular safety concern when the product was used at the proposed labeled maximal dose of 250 mcg (After 1 inhalation, wait 1 minute. If symptoms not relieved, take a second inhalation by repeating shake then spray into the air once before inhalation), giving some idea of the safety margin available in the case of overdose importantly when the product may be used at higher doses than recommended, or if a superpotent dose should be delivered with an actuation.

Human Factors (Behavioral) Study

Sections 1.1 and 2 discussed the information needed to support epinephrine HFA marketing focusing on elements that differed from the previously available epinephrine CFC Primatene Mist product label. Information was needed from the human factors behavioral study based on the consumer understating of labeled packaging instructions, including the DFL, and the consumer instructions for use to determine safe and effective use of the product with the objective of minimizing use errors to the lowest possible level when the epinephrine HFA product was used in the nonprescription setting without the oversight of a learned intermediary.

Response to FDA's December 23, 2016 Complete Response Action Letter

DNDP provided several labeling recommendations during the second cycle NDA review prior to the complete response letter issuance that were already adopted by Armstrong in the DFL, the consumer instructions for use, and the outer carton.

Armstrong drastically modified the consumer instructions for use from what was used in the human factors study G3, with simplified steps so that information was now presented only on one side of the page, and aligning the instructional language on the actuator to the revised DFL and consumer instructions for use. Carton box modifications were made requiring the consumer instructions for use information insert to be removed prior to using the inhaler. Information from the CMC bench studies, conducted prior to human factors study G4, supported the revised information in the instructions for use tested in human factors study G4. Armstrong additionally modified the labeling on the device actuator and mouthpiece with pictograms incorporating DNDP recommendations considering that the user may not have immediate access to the DFL or consumer instructions for use when the inhaler is being used. Re-testing these changes in a human factors study was considered necessary because there were no prescription inhaler products with a similar presentation. DNDP considered it a reasonable approach to proceed with human factors testing given that the major elements being tested were related to instructions for use. Because the DFL and consumer instructions for use were changed substantially after the previous label comprehension studies, the human factors study was much more relevant to the overall expected use of the product by consumers.

Please refer to Grace P. Jones, PharmD, BCPS, Division of Medication Error Prevention and Analysis (DMEPA) review and recommendations of the human factors validation study report G4. DMEPA noted that the human factors validation study G4 results demonstrated that the intended user population can use the proposed epinephrine HFA product safely and effectively. DMEPA provided editorial recommendations for maintaining consistency with the information across the various labeling pieces.

Reviewer comments

Assessment of the three primary critical tasks tested in the human factors validation study G4 were found acceptable during DMEPA review, to inform labeling:
Task 1: initial prime –shake then spray into the air 4 times.
Task 2: routine use (dosing) –shake the inhaler before taking a dose
Task 3: washing procedure –rinse water through both ends of the mouthpiece for at least 30 seconds

Initial prime –shake then spray into the air 4 times

Anticipating clinical situations during product use, as was shown in the human factors study G4, some participants did not adhere to the labeled instructions to shake then spray into the air four times for initial prime or activation of the epinephrine HFA metered dose inhaler. While all participants in human factors study G4 met the minimal acceptance criteria to at least shake then spray one time (epinephrine HFA proposed labeling states shake then spray into the air four times), performance of the (minimal) shake then spray one time procedure was shown in the CMC bench data to result in a partial or suboptimal or subpotent delivery of first dose administered (i.e., for the emitted second spray). Failure to deliver a dose of a rescue inhaler during an acute asthma attack could result in serious outcomes if the consumer is unable to seek immediate medical assistance. However, the labeled directions permit a repeat or additional dose after one minute for asthma relief, and this label permitted second dose will provide the therapeutic dose as per the reviewed CMC bench data (i.e., for the emitted third spray). Concern of administering a superpotent dose or overdose in the absence of performance of labeled task 1 or routine use task 2 may result in an increased incidence of adverse effects, although the products safety profile discussed above did not identify serious safety signals based on the higher systemic exposures observed.

Inhaler repriming frequency for routine use

Shaking (Task 2) is critical for adequate therapeutic dose administered during intermittent episodes of asthma for the temporary relief of mild symptoms experienced because of the suspension nature of the epinephrine hydrofluoroalkane metered dose inhaler product.

Armstrong's August 2017 submission stated that in the inverted position (the position that the inhaler is held during use), the Active Pharmaceutical Ingredient (API) (b) (6)

Figure 1: Inverted Orientation of Epinephrine HFA MDI at Storage and at Use

Position	Orientation at Storage (not Spray)		Orientation at Use (at Spray)	
	Inhaler Unit	Canister Unit	Inhaler Unit	Canister Unit
Inverted	(b) (4)			

Source: eCTD submission \\CDSESUB1\evsprod\NDA205920\0065, (August 17, 2017). Module 1.11.4. Supplemental Device Study Report for Under and Supra-Therapeutic Dosing Risk Evaluation due to User Error of "No Shaking". Table 1: Three (3) Positions of Storage.

Shaking minimizes the risk for variability in the dose provided and variability in the dose content uniformity such that settled suspension becomes uniform and provides the most optimal dose for the user. Not shaking the inhaler before first use (initial priming stage) or during routine use (repriming or prior to taking the dose) will result in either subpotent dose or superpotent dose.

The label reviewed during the June 28, 2016 (Class 2 resubmission) review cycle included evaluation of the task to spray after shaking prior to dosing (repriming), and this information in labeling was considered acceptable. After issuance of the December 23, 2016 complete response, Armstrong made considerable improvements to the consumer instructions for use and the actuator label including simplified labeling instructions. Human factors study G4, task 2, evaluated if the newly proposed user interface, (b) (4)

Dr. Ramaswamy noted that the epinephrine HFA inhaler (b) (6) the emitted dose content of the first dose from the inhaler may be lower than the expected after a period of non-use (after the task 1 initial prime –shake then spray into the air 4 times), resulting in underdosing or delivering a subpotent dose. Armstrong obtained repriming frequency data from more than one study simulating use conditions (b) (4)

(b) (4) I concur with Dr. Ramaswamy's conservative labeling recommendation to reprime before each time the epinephrine HFA is used to administer a dose, to provide consistent therapeutic dosing.

After the initial priming activation step when the product is initially obtained, considering the information from the various supportive CMC bench data reviewed, DNDP is recommending the most conservative labeling directions for each subsequent dosing. More importantly *repriming* or reactivating the device with shaking *and spraying* in the air prior to each inhalation (b) (4) is considered for optimal use.

Inhaler Washing/Cleaning frequency

(b) (4) CMC bench study data obtained since the December 23, 2016 complete response action, which indicated that the use of dirty inhalers beyond seven days of use without cleaning will result in the delivery of inconsistent dose.

The new CMC bench study data reviewed did not report actuator clogging indicating that the risk of subpotent dosing is low over the container life, as the delivered dose content did not gradually decrease over the twenty days simulated use period without cleaning. When the average dose content of the first two sprays dispensed was taken together, utilizing supporting labeled information that permitted administration of a second dose after a minute of inadequate relief of the asthma symptoms, the two spray CMC bench study data did not show evidence of subpotent doses delivered, and therefore was reassuring. However, without washing the actuator beyond seven days may result in situations when the asthmatic will likely receive superpotent dosing, especially with the first of two recommended inhalations per the labeled instructions for use. There is medication build-up or accumulation resulting in higher than expected dose content due to dose carry over from the actuator.

Dr. Ramaswamy's September 27, 2018 CMC review additionally included information comparing the orifice diameter of the proposed epinephrine HFA actuator (b) (4) mm) to other albuterol sulfate aerosol inhalers ((b) (4) mm) that discussed drug load per actuation and alcohol content of the proposed epinephrine HFA actuator during simulated use for the inhaler life of 160 sprays over 20 days explaining that the proposed epinephrine HFA product did not appear to clog in comparison to other commercially available inhalers. Based on Armstrong's experimental data shown in Table 2, it appears the orifice diameter for the proposed epinephrine HFA product is (b) (4) than that for the albuterol HFA metered dose inhaler products.

Table 2: Comparison of Epinephrine HFA MDI and Albuterol HFA MDI

Product	Proventil HFA	ProAir HFA	Epinephrine HFA
Formulation			
API name	Albuterol Sulfate	Albuterol Sulfate	Epinephrine
Amount of alcohol, %	(b) (4)		1.0%
Delivery amount per spray			
Total amount per actuation, mg	(b) (4)		
Actuator orifice			
Diameter of orifice, mm			
Section area of the orifice			
Ratio of orifice section area, vs. ProAir			

Source: eCTD submission \\CDSESUB1\evsprod\NDA205920\0065, (August 17, 2017). Module 1.11.4. Supplemental Device Study Report for Under-Dosing Risk Evaluation, Table 4.
*from experimental data

During several rounds of review discussions and labeling meetings, the review team agreed that the consumer's benefitted from washing the inhaler more frequently (b) (4) to provide consistent dosing and for maintaining a clean device for subsequent uses. Dr. Ramaswamy's CMC product quality review discussed that while the original (previously conducted) cleaning study data supported three days of use without inhaler cleaning and the recently reviewed data suggested seven-day interval wash frequency, the originally proposed labeling instruction in the June 28, 2016 (Class 2 resubmission) "Wash every day if used" was very conservative. Recommendation to instruct consumers to wash the inhaler after "each day of use" was found acceptable by the review team instead of the proposed (b) (4) (b) (4) the more conservative and direct reminder to wash after each day of actual use was optimal for safe and effective use.

Number of Actual Doses Available per Epinephrine HFA Nonprescription Labeling

During internal meetings for NDA 205920 class 2 resubmission the review team discussed the proposed number of actuations per inhaler (160 sprays) considering the concerns raised during the joint meeting of the Nonprescription Drugs and Pulmonary-Allergy Drugs Advisory Committees (February 25, 2014) that the availability of a high number of actuations per inhaler could encourage continued use for prolonged durations that may result in delayed 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 healthcare provider for managing their asthma. Please refer to prior NDA 205920 clinical review of Ryan

Raffaelli, MD (April 15, 2014; DARRTS Reference ID: 3489745) section 9.3 for the summary of these deliberations by the advisory committee.

DNDP's determination for approvability of epinephrine HFA for nonprescription use took into consideration the number of doses for marketing based on the national guidelines for asthma management developed by the National Institutes of Health (NIH)[3], product labeling, the Advisory Committees' deliberations and data submitted in the NDA.

For any packaging recommendations to mitigate or limit the available inhalations per epinephrine HFA metered dose inhaler, DNDP considered the information for the labeled steps which included the initial metered dose inhaler activation (wasting 4 priming sprays), and accounting for the subsequent repriming steps (80 repriming sprays) prior to each dosing. Of the 160 total sprays, the proposed inhaler presentation is expected to provide 80 usable inhalations suitable for 10 days of labeled nonprescription use, i.e., 10 x 8 sprays per day based on labeled recommendation for no more than 8 inhalations in 24 hours.

The NIH guidelines for the diagnosis and management of asthma classify asthma severity as intermittent when symptoms occur on two or fewer days per week, which is the targeted population for the nonprescription epinephrine HFA metered dose inhaler use, for "the temporary relief of mild symptoms of intermittent asthma." When used as recommended up to the maximum recommended eight inhalations during a 24 hour period, and while adhering to warnings to see a doctor when experiencing more than two asthma attacks in a week, the epinephrine HFA metered dose inhaler user may use up to 16 inhalations in a week. Therefore, during a month, for the symptomatic control of intermittent asthma symptoms based on the conservative labeling recommendations per the DFL and consumer instructions for use, 64 usable inhalations are suitable for eight days of labeled nonprescription use. As discussed above, the proposed inhaler presentation is expected to provide 80 usable inhalations suitable for 10 days of labeled nonprescription use, i.e., 2 more days of use.

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

[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 8, 2018)

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) 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 situations whereby prospective nonprescription users of the proposed epinephrine HFA product who have been diagnosed previously with asthma (as per the epinephrine HFA label) and choose to not have their asthma care further managed by a healthcare provider because of the availability of epinephrine HFA for nonprescription use, alternate packaging configurations are to be considered. 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.

9. Advisory Committee Meeting and Other External Consultations

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 nonprescription use setting. Please refer to Ryan Raffaelli, MD (April 15, 2014; DARRTS Reference ID: 3489745) NDA 205920 clinical review for the advisory committees' deliberations and for summary discussions and comments for considering the proposed epinephrine HFA metered dose inhaler for approval. 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 September 26, 2018).

10. Labeling Recommendations

10.1. Nonprescription Drug Labeling

The proposed DFL for epinephrine HFA provides indication for "the temporary relief of mild symptoms of intermittent asthma" which includes patients with intermittent asthma only. In addition, the label contains a "Do not use unless a doctor said you have asthma." This indication and warning are consistent with the previously marketed epinephrine CFC product. Labeling discussions and recommendations have been discussed in several sections of the review. Please see separate DNDP labeling reviews, that include review and recommendations for the proposed website and the instructional videos.

11. Risk Evaluation and Mitigation Strategies (REMS)

Routine postmarketing surveillance is appropriate.

12. Postmarketing Requirements and Commitments

Please refer to prior NDA 205920 clinical review of Ryan Raffaelli, MD (December 19, 2016; DARRTS Reference ID: 4026312) section 1.4 for the recommendations requiring pediatric studies under the Pediatric Research Equity Act (PREA).

DNDP discussed NDA 205920 with the FDA's internal 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, therefore clinical studies in this age group would be impossible or highly impracticable.

Required PREA studies included the conduct of deferred multiple dose safety and efficacy trial with three arms in 4 to 11 years old pediatric subjects with asthma comparing a two-inhalation dose of the test product epinephrine inhalation metered dose inhaler (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. PeRC did not consider it necessary to conduct a separate PK study, as discussed in Jianmeng Chen, MD PhD December 9, 2016 clinical pharmacology review.

13. Appendices

13.1. References

See footnote references and in-text references.

13.2. Financial Disclosure

Not applicable.

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/

SUHAIL KASIM
10/22/2018

JENNY L KELTY
10/22/2018

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205920
Priority or Standard	Standard
Submit Date(s)	June 28, 2016
Received Date(s)	June 28, 2016
PDUFA Goal Date	December 23, 2016
Division / Office	DNDP/ODE IV
Reviewer Name(s)	Ryan Raffaelli
Review Completion Date	December 12, 2016
Established Name	Epinephrine Inhalation Aerosol
(Proposed) Trade Name	Primatene Mist
Therapeutic Class	Nonselective adrenergic receptor agonist/ bronchodilator
Applicant	Armstrong Pharmaceuticals, Inc.
Formulation(s)	Aerosol, metered (125 mcg/ inhalation)
Dosing Regimen	1-2 inhalations every 4 hours as needed; maximum 8 inhalations/24 hours
Indication(s)	Temporary relief of mild symptoms of intermittent asthma

Intended Population(s) 12 years of age and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

No clinical data were submitted in this application, thus, this reviewer relinquishes recommendation on regulatory action to a synthesis of the other discipline reviews.

The following were deficiencies outlined in the Complete Response Letter of May 22, 2014:

1) FDA required resolution of post-inspection current good manufacturing practice (cGMP) deficiencies at the (b) (4) facility
2) Data supporting safety of chronic inhalation of thymol is required
3) Labeling requires significant revision and testing in label comprehension study to ensure understanding of certain critical information: priming before first use, daily cleaning when used, repriming when the inhaler is wet, not to rely on the dose indicator if dropped, disassembly/reassembly for cleaning, pressing on the center of the indicator for dosing, and orientation of the inhaler during use and storage
4) FDA required behavioral testing (human factors) with optimized labeling to reassess ability to use and properly care for the product
5) FDA required a randomized actual use trial to quantify and analyze problems with use and characterize sources of error. We recommended that randomization take place with a marketed bronchodilator product comparator.

*Reviewer's comments: With regard to #5, the actual use trial, FDA and the applicant discussed the need for one at a Type A meeting following the Complete Response (see **Section 2.5** below for details on the pre(re)submission regulatory activities).*

Since no clinical data were submitted for review, the findings from label comprehension studies (Ms. Cohen's and Dr. Zhao's reviews), the human factors study (reviews by Drs. Jones and Zhao), nonclinical study (Dr. Thompson's review) and the quality assessment (Dr. Muthukumar's review) will inform the recommendation on regulatory action.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

If approved, a partial waiver is acceptable, and an additional pediatric trial is required under the Pediatric Research Equity Act (PREA). Similar to the first review cycle, the applicant submitted a request for partial waiver of trials in children under the age of four. Trials in this age group would be impossible or highly impracticable (Section 505B(a)(4)(A)(i), Federal Food, Drug and Cosmetic Act (FD&C Act). Children under 4 years do not have the dexterity or coordination of efforts to reliably manipulate the inhaler device. In fact, nebulized medications are cornerstones of current practice in this population. Additionally, national guidelines, particularly the National Asthma Education and Prevention Program (NAEPP, NIH), indicate that asthma is difficult to diagnose in children under four years. The Pediatric Review Committee (PeRC) agreed with the partial waiver.

The applicant must conduct a multiple dose safety and efficacy trial with three arms in pediatric subjects with asthma 4 to 11 years of age comparing a two-inhalation dose of the test product, epinephrine inhalation aerosol (125 mcg/inhalation), a one-inhalation dose of the test product, and placebo. The trial must include an assessment of epinephrine exposure around Tmax (b) (4) See the brief review by Dr. Chen (Office of Clinical Pharmacology) with further discussion about the PK component of the trial. (b) (4) Consistent with the timeline (letter of April 9, 2014) proposed by the applicant regarding submission of final study reports during the first review cycle, PeRC agreed that one year post-approval was reasonable to submit a protocol for review, conduct the trial and submit a final report. Thus, if approved, a final study report would be submitted in January 2018. However, this is negotiable with the applicant to come to agreement on a reasonable timeline.

The PeRC met on November 16, 2016 to discuss this application and agreed with the division on deferral of the required trial and the partial waiver.

2 Introduction and Regulatory Background

Since there were no clinical data submitted, this document only provides a brief update of regulatory activities since the Complete Response, comments on the proposed labeling (**Section 9.2**) and a statement about required postmarketing pediatric studies under PREA. Information in this officer's original review document will not be repeated here. Numbering for this review follows the clinical template, but missing headers are purposeful and not relevant to this review.

2.1 Product Information

See this medical officer's clinical review of April 15, 2014 (DARRTS) for details on product and presubmission regulatory activities.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Following the Complete Response, the applicant requested a meeting with FDA held on October 1, 2014. At the meeting, we discussed assessment of thymol safety and the need for data on comprehension of important labeling messages to ensure proper use of the product. The applicant committed to addressing all deficiencies listed in the Complete Response letter. With regard to #5 in **Section 1.1**, FDA deferred discussion of an actual use trial until it had an opportunity to review findings from the label comprehension and human factors assessments. FDA advised the applicant to request a meeting to determine if an actual use trial was needed. At that time, the applicant agreed. In May 2016, the applicant submitted the protocol for study G3, the human factors assessment, to the IND (74286). The next formal communication with the applicant and document submission included the application resubmission for approval.

Reviewer's comment: The applicant declined to seek advice on designing and conducting an actual use trial. This was their prerogative, but as noted above, consideration of such a trial was our advice to which the applicant initially agreed.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the quality of the electronic submission was adequate. The sections reviewed were reasonably well-organized with working hyperlinks for ease of review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

See Cross Discipline Team Lead, Dr. Frank Becker's, review and the original clinical reviews.

5 Sources of Clinical Data

No clinical data submitted.

6 Review of Efficacy

See original clinical reviews.

7 Review of Safety

See original clinical reviews.

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/s/

RYAN M RAFFAELLI
12/12/2016

FRANCIS E BECKER
12/19/2016

CLINICAL REVIEW

Application Type	505(b)2
Application Number(s)	205920
Priority or Standard	Standard
Submit Date(s)	July 17, 2013
Received Date(s)	July 22, 2013
PDUFA Goal Date	May 22, 2014
Division / Office	DNCE/ODE IV
Reviewer Name(s)	Ryan Raffaelli, M.D.
Review Completion Date	April 15, 2014
Established Name	Epinephrine inhalation aerosol
(Proposed) Trade Name	*pending
Therapeutic Class	Nonselective adrenergic receptor agonist/ bronchodilator
Applicant	Armstrong Pharmaceuticals, Inc.
Formulation	Aerosol, metered (125 mcg/ inhalation)
Dosing Regimen	1-2 inhalations every 4 hours as needed; maximum 8 inhalations/24 hours
Indication	Temporary relief of mild symptoms of intermittent asthma
Intended Population(s)	12 years of age and older

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1 Recommendations/Risk Benefit Assessment

Armstrong Pharmaceuticals (Armstrong) seeks 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 is proposed for the temporary relief of mild symptoms of intermittent asthma. This is a similar indication as that approved by FDA in 1967 for a predicate OTC product, Primatene® Mist (Primatene Mist), also an epinephrine inhalation aerosol. That product was removed from marketing in 2011 because it contained a chlorofluorocarbon (CFC) propellant which was banned around the world following ratification of the Montreal Protocol (U.S. ratification - 1988). Primatene Mist was not removed from the market for reasons of safety or effectiveness.

While clinical guidelines supported by national medical associations (**Section 2.6 Other Relevant Background Information**) generally point to asthma management as care centered on the clinician and patient, Primatene Mist was available for several decades in the OTC setting with a favorable postmarketing safety experience (see **Section 8 Postmarket Experience**). As an OTC product, there was no requirement for involvement of a learned intermediary advising on safe and proper use. Based on its experience with Primatene Mist, the applicant believes that its product is safe and effective for the claimed indication, and that an important medical need exists for OTC availability of a quick-relief asthma treatment.

1.1 Recommendation on Regulatory Action

From the clinical perspective, and with specific focus on the postmarketing experience of Primatene Mist in the OTC setting, this reviewer recommends approval with acceptance of proposed labeling changes (see **Section 9.2 Labeling Recommendations, Section 1.2**). However, due to the differences between Primatene Mist and the proposed epinephrine HFA, extrapolation of post-marketing safety from Primatene Mist to the proposed product must be interpreted with caution.

My recommendation is based on a portion of the available data pending a joint decision on the appropriate regulatory action from the Division of Nonprescription Clinical Evaluation (DNCE) and the Division of Pulmonary, Allergy and Rheumatology Products (DPARP). This reviewer did not review in detail the clinical efficacy trials, the device and dose indicator performance assessment or the label comprehension and human factors evaluations. See the DPARP (Dr. Pippins), Office of Biostatistics (OB; Ms. Zhao), Office of New Drug Quality Assurance – Chemistry, Manufacturing, Controls (ONDQA - CMC; Dr. Ramaswamy) and DNCE-social science (Ms. Cohen) reviews. See also the voting record and summary from the February 25, 2014 Joint Advisory Committees' Meeting (**Section 9.3 Advisory Committee Meeting**). There, the panelists discussed several significant and potentially significant issues including

limitations and incompleteness of submitted data and concern about the reliability of the device and dose indicator. The totality of available information will drive the regulatory decision on whether the proposed product will be approved for OTC marketing.

1.2 Risk Benefit Assessment

Efficacy

The applicant believes that its epinephrine HFA is an effective and needed OTC product for quick-relief management of asthma. In addition to conducting clinical trials to support this NDA (see Dr. Pippins' and Ms. Zhao's reviews), the applicant stands by the several decades of OTC availability of the approved and previously marketed Primatene Mist product to support the effectiveness of epinephrine inhalation for relief of bronchospasm. The clinical trials included:

- Two phase 2 single-dose, dose-ranging trials (E004-A and A2)
- Three single-dose, clinical PK trials (E004-B, B2 and B3)
- A three month phase 3 efficacy trial (E004-C) with a three month safety extension (E004-C2)
- One four week pediatric efficacy trial (E004-D)

Effectiveness, i.e., whether the efficacy of the product is generalizable to OTC consumers in 'real world' use, was assessed in studies of consumer behavior:

- Label Comprehension Study (E004-F)
- Behavioral (Human Factors) Study (E004-G)

However, epinephrine HFA differs from Primatene Mist in several important ways (**Table 1** in **Section 2.1 Product Information**). A complete assessment of effectiveness of the proposed product in the OTC setting must include a determination of whether the device and dose indicator reliably perform over the lifespan of the product, and whether consumers can use the product safely and properly to achieve the intended effect, i.e., relief of mild symptoms of intermittent asthma. Dr. Pippins, Dr. Ramaswamy, and Ms. Cohen address these issues.

Safety

The applicant relies on safety data from completed clinical trials, postmarketing experience from several decades of OTC availability of Primatene Mist and data from assessment of label understanding and behavior to ensure that consumers are capable of using the product safely. Safety data to support this application come from the following sources:

- The dose-ranging, clinical PK and efficacy trials listed above
- Pharmacodynamic evaluation at high dose (clinical PK trials B, B2 and B3)
- Studies E004-F and -G

- Applicant's pharmacovigilance data (2008-2012)
- FDA-Adverse Event Reporting System (AERS) data (1997-2013)
- American Association of Poison Control Centers – National Poison Data System (2008-2012)
- Published literature

Safety data from the dose-ranging, clinical PK, and clinical safety and efficacy trials are reviewed by others, although I briefly summarized a consult review conducted by Dr. Tom Marciniak in the Division of Cardiovascular and Renal Products (DCRP) (**Section 4.4.2 Pharmacodynamics**). He reviewed cardiovascular safety, from conducted clinical trials, focusing on the high dose PK trials to determine whether there were safety concerns, particularly if the product is overused. His overall assessment was that the data were reassuring that no significant cardiovascular effects are likely to occur when the product is used as directed. However, overuse may result in clinically significant blood pressure and heart rate changes, expected effects of epinephrine.

Enrollment in the phase 3 trials included 373 adult and adolescent subjects. Over 66% (248/373) were exposed to one or more doses of epinephrine HFA for up to six months. Additionally, thirty five pediatric subjects (4-11 years of age) were exposed to multiple doses in Trial D. Applicable data from label comprehension and human factors evaluation (1406 subjects), and device and dose indicator performance and reliability are evaluated by others as well.

This reviewer was tasked with specific focus on postmarketing experience from Primatene Mist availability cautiously extrapolated to the proposed product. Distribution of Primatene Mist over four years, from 2008-2011, was 18.5 million units. The applicant submitted line listings and select narratives for a total of 1174 adverse events (AEs), including 1034 serious events (SAEs), over a 16 year period (1997-2013) from its database and FDA's AERS. From the overall assessment of the data, this reviewer investigated events that signaled inappropriate use of Primatene Mist, e.g., lack of effect reports with narratives suggesting use for more than mild symptoms, overuse by number or frequency of inhalations, and abuse. I also specifically reviewed cardiac-related cases and pediatric cases since Primatene Mist was approved for use by children as young as four. While the applicant proposes that epinephrine HFA would be marketed only for children older than 12 years (**Section 7.6.3 Pediatrics and Assessment of Effects on Growth**), historical familiarity with Primatene Mist (labeled for 4 years and older) could lead to off-label use. None of these investigations identified any safety concerns. Overall, compared to the extent of distribution, the number and significance of events are minimal (**Section 8 Postmarket Experience**).

Asthma Treatment

In addition to analysis of submitted data for this product, we must also consider more generally whether it is appropriate to make available an epinephrine inhaler, or any

quick-relief product, for OTC asthma treatment. Asthma is a chronic disease affecting millions in the U.S. It is classified into four categories based on several factors. Intermittent asthma, the category of interest for the proposed product, is diagnosed in adults and children over age 12 if they[1]:

- have normal baseline lung function
- have symptoms ≤ 2 times per week
- use short-acting beta-agonists ≤ 2 times per week
- have nighttime awakenings ≤ 2 times per month
- have no interference with daily activities
- experience ≤ 1 exacerbation per year, and
- do not have an alternative diagnosis

Intermittent asthma sufferers may have mild, moderate or severe exacerbations, but short-acting beta-agonists should still be effective to relieve symptoms. Epinephrine HFA is a short-acting, non-selective, beta-agonist intended as a quick-relief product for mild asthma symptoms. National guidelines (**Section 2.6 Other Relevant Background Information**) identify inhaled, short-acting, selective beta$_2$-agonists as treatments of choice for acute management of bronchospasm. Because of their selectivity, prescription products such as albuterol and levalbuterol limit potential systemic side effects (heart rate increase, blood pressure increase, tremor, hyperglycemia and hypokalemia). Non-selective beta-agonists, such as epinephrine, are more likely to cause such effects and are, therefore, not recommended in the guidelines. As indicated above, however, until 2011 epinephrine had been available as Primatene Mist for over 50 years in the OTC setting without significant safety findings. Further, proposed labeling for epinephrine HFA contains similar warnings and instruction as Primatene Mist. Other labeling recommendations are offered in (**Section 9.2 Labeling Recommendations**). DNCE and DPARP will take national guidelines, labeling, the Advisory Committees' deliberations and data submitted in the NDA under consideration to determine approvability of epinephrine HFA for OTC use.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

If epinephrine HFA is approved, this reviewer recommends that additional pediatric trials be conducted under a postmarket requirement (PMR) as per the Pediatric Research Equity Act (PREA). The applicant submitted a request for a partial waiver of trials in children under the age of four. The applicant contends that trials in children under four

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 March 25, 2014)

are impossible or highly impracticable (Section 505B(a)(4)(A)(i), Federal Food, Drug and Cosmetic Act (FD&C Act)). It states that these children have not yet developed the dexterity and coordination of efforts to adequately use the device for its intended purpose. Notably, Primatene Mist was approved for use by adults and children as young as four due to safety concerns for children younger than four. Also, national guidelines, particularly the National Asthma Education and Prevention Program (NAEPP, NIH)[1], indicate that asthma is difficult to diagnose in children under four.

This reviewer finds an alternative statutory reason to waive pediatric trials. Approved, prescription-only drug products, short-acting $beta_2$-agonists and inhaled corticosteroids, exist for use by children less than four years of age to manage asthma-related reversible bronchospasm. Section 505B(a)(4)(A)(iii) of the FD&C Act applies more closely to supporting a waiver for trials in children less than 4 years of age. The statute states that trials may be waived if a product fails to represent a meaningful therapeutic benefit over existing therapies for certain pediatric patients and is unlikely to be used in a substantial number of these patients. Children less than 4 years old may use prescription-only drug products and, since asthma is considered difficult to diagnose in children under age four, it is unlikely that a substantial number of children in this age group would use epinephrine HFA in the OTC setting. Involvement of a learned intermediary is an important component of asthma care for these children.

As previously discussed with the applicant, this reviewer recommends the following PMR which will be presented to Pediatric Research Committee (PeRC):

- Waive trials in children < 4 years of age
- (b) (4)
- (b) (4) one multiple-dose safety and efficacy trial in children with asthma 4 to <12 years of age

*Reviewer's comments: Prior to submission of this NDA, FDA asked the applicant to submit any available pediatric data regardless of whether it chose to seek approval for the studied population. The applicant submitted Trial E004-D (see **Table 7**), a trial in children 4-11 years of age. The trial failed to meet its primary endpoint, but exploratory analysis prompted the applicant to re-design protocols to better assess efficacy in the pediatric population. See **Section 7.6.3 Pediatrics and Assessment of Effects on Growth** for additional discussion of pediatric concerns.*

The applicant proposes that final trial reports will be submitted approximately 18-20 months after approval of the NDA for adults and children as young as 12.

Reviewer's comments: The PeRC meeting to discuss PREA requirements is scheduled for April 30, 2014. The results of our discussion with the committee are not included here. The meeting was originally scheduled to occur prior to finalization of this review; however, we asked the applicant to provide more information on its proposed pediatric

plan. The applicant's original plan lacked sufficient details to assess adequacy. Our request prompted a rescheduling of the PeRC meeting.

2 Introduction and Regulatory Background

2.1 Product Information

- Established name and proposed trade name: Epinephrine Inhalation Aerosol (b) (4) is the established name. The proposed tradename, (b) (4) is undergoing evaluation, but is unlikely to be allowed.

Reviewer's comment: FDA denied the initial proposed tradename, (b) (4) At that time, it stated that (b) (4) I will continue to refer to the product as epinephrine HFA.

- Pharmacologic class: Bronchodilator (nonselective adrenergic receptor agonist)

Epinephrine HFA is a proposed replacement for Primatene® Mist (Primatene Mist) as an OTC bronchodilator for relief of mild symptoms of intermittent asthma. The applicant was required to cease marketing and distribution of Primatene Mist in December 2011 (**Section 2.3 Availability of Proposed Active Ingredient in the United States**). The proposed indication is similar to Primatene Mist's, that is, temporary relief of mild symptoms of intermittent asthma including wheezing, tightness of chest and shortness of breath. Primatene Mist was indicated for temporary relief of occasional symptoms of mild asthma. The former is a more accurate depiction of the symptoms and severity of disease applicable to this NDA. The applicant proposes a modified dosing regimen, compared to Primatene Mist's regimen, based on the pharmacokinetics of this more systemically available form of epinephrine (**Sections 4.4.3 Pharmacokinetics** and **4.4.2 Pharmacodynamics**). It also proposes use of the product for adults and children down to 12 years of age whereas Primatene Mist was indicated for children as young as four years (**Section 7.6.3 Pediatrics and Assessment of Effects on Growth**). There are several additional differences between Primatene Mist and the proposed epinephrine HFA product (see **Table 1** and **Figure 1**).

Table 1: Comparison of Primatene Mist and Epinephrine HFA Inhalers

Parameter	Primatene® Mist	Epinephrine HFA
Propellant	CFC	HFA
Drug container	Glass reservoir	Aluminum canister
Dose indication	Semi-transparent reservoir	Attached dose indicator
Formulation	Solution	Suspension
Use and care instructions	Clean mouthpiece after each use	Prime in certain situations; Shake prior to each use; Disassemble and clean daily
Population	Age 4 years and above	Proposed age 12 and above
Dosing regimen	1-2 inhalations (inh.) every 3 hours	1-2 inh. every 4 hours; maximum 8 inh. per day
Other		Greater systemic exposure

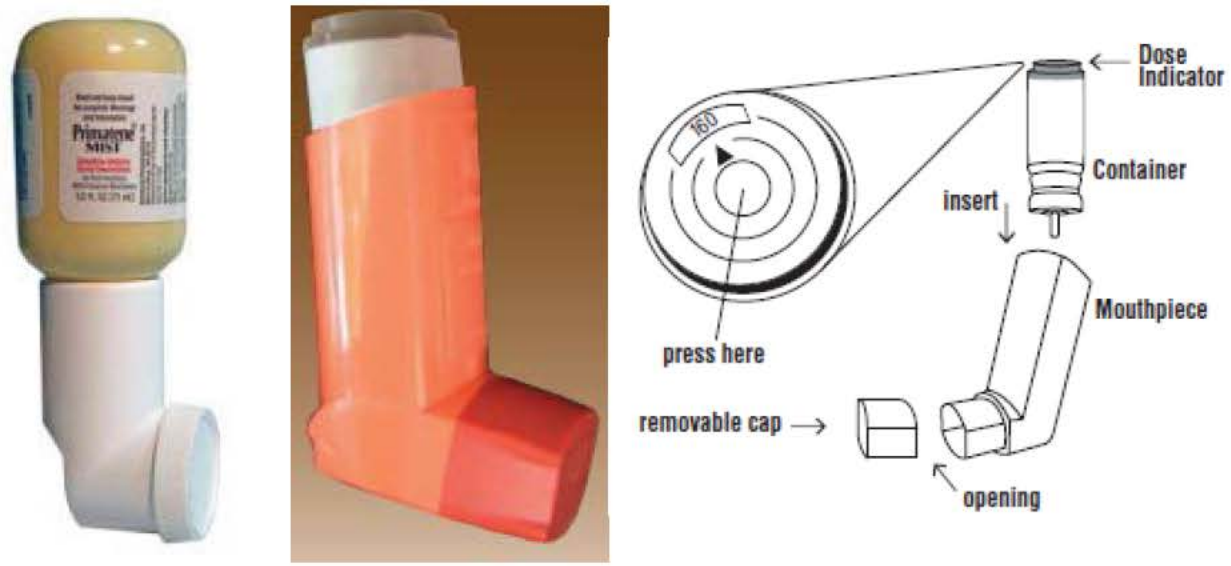


Figure 1: Images of Primatene Mist (Left) and Proposed Epinephrine HFA with Diagram

(Sources: http://primatene.com/products/index.asp and appendices 1 & 2 from Applicant's briefing document for February 25, 2014 meeting of Joint Nonprescription Drugs and Pulmonary-Allergy Drugs Advisory Committees)

The difference in propellants shown in **Table 1** has implications for use and care instructions. Whereas certain CFCs limited device clogging by having the capacity to nearly self-clean, MDIs with HFA propellants are more prone to clogging due to the stickiness of HFAs. Further, the suspension formulation of the epinephrine HFA adds to

the potential complexity of proper use in the OTC setting. The epinephrine HFA inhaler must be shaken vigorously for several seconds before each use and primed regularly – before first use, if not used in more than two days, if wet after cleaning and if dropped. Also note that if the inhaler is dropped, the dose indicator is no longer reliable and consumers will be directed, through labeling, to keep track of the number of uses. As in **Figure 1**, the Primatene Mist inhaler included housing of the drug in a semi-transparent, plastic-coated glass reservoir. No dose indicator was incorporated into the device since consumers could view the drug within the reservoir. In 2003, FDA finalized guidance recommending that new MDIs for oral inhalation have an integrated dose-counting device (*Guidance for Industry – Integration of Dose-counting Mechanisms into MDI Drug Products* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071731.pdf). This is important because a reliable counter or indicator minimizes both waste, by limiting the number of MDIs discarded because users believed they were empty when they may still contain adequate metered doses (overcounting), and risk, by ensuring that users do not rely on a product beyond the recommended number of true metered doses (undercounting). The epinephrine HFA is proposed to include an opaque aluminum canister, and since we are considering it for OTC use as a quick relief product, assurance that it will provide an appropriate treatment dose is clinically relevant. Notably, the dose indicator for epinephrine HFA is an add-on, and is not integrated into the device.

Reviewer's comment: Issues with the device's and dose indicator's accuracy and robustness are addressed in more detail in the CMC and DPARP reviews and briefly summarized in ***Section 9.3 Advisory Committee Meeting*** *as the issues constituted a significant portion of the discussion at that meeting. Also of concern are the differences in the proposed directions for use and care compared to those of Primatene Mist. If approved, former Primatene Mist users may assume that epinephrine HFA can be used in an identical way. Data from consumer behavior studies suggested to the applicant that there may be confusion in understanding the differences between how to use the epinephrine HFA product and Primatene Mist, prompting it to propose additional labeling statements to the product carton (***Figure 2***; image that begins "See Side Panel…").*

Also related to proper use, the product must be cleaned daily while in use. Primatene Mist's label directed consumers to perform only minimal mouthpiece cleaning after each use. The cleaning instructions are more involved for epinephrine HFA (see **Section 9.2 Labeling Recommendations**).

Finally, the applicant proposes to initially market the product for adults and children as young as 12 years while it completes ongoing trials and data analysis to evaluate safety and efficacy in children as young as four. It has requested a deferral to complete those trials (see **Section 7.6.3 Pediatrics and Assessment of Effects on Growth**).

*Reviewer's comments: This reviewer is concerned that former users or parents/guardians of users of Primatene Mist will be familiar with that product's approved indication for use by children as young as four years of age and use it off-label. While there are minimal postmarketing data indicating that use, even off label by children younger than 12, will result in a significant safety risk (see **Section 8***

Postmarket Experience*), we are aware of data which raises questions as to the efficacy of the product for children under 12 (****Section 7.6.3 Pediatrics and Assessment of Effects on Growth****).*

2.2 Tables of Currently Available Treatments for Proposed Indications

There are both prescription-only (Rx) and OTC drug products approved or allowed to be marketed under a Final Monograph (21 CFR 341 at 341.16; Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-counter Human Use) for similar indications, as quick or temporary relief products for treatment of bronchospasm due to asthma with symptoms including shortness of breath, tightness of chest and wheezing. **Table 2** shows available Rx and OTC products marketed for management of asthma-related symptoms.

Table 2: Currently Available Approved and Allowable Treatments for Symptoms of Asthma

Drug Substance	Dosage Form(s)	Rx or OTC
Albuterol sulfate	Multiple dosage forms	Rx
Ephedrine (multiple salts)	Oral dosage forms	OTC
Epinephrine (multiple salts)	Aqueous solution in hand held rubber bulb nebulizer*	OTC
Levalbuterol (hydrochloride/ tartrate)	Inhalation solution/ Metered inhalation aerosol (tartrate)	Rx
Metaproterenol sulfate	Multiple dosage forms	Rx
Pirbuterol acetate	Metered inhalation aerosol	Rx
Racephedrine hydrochloride	Oral dosage forms	OTC
Racepinephrine hydrochloride	Aqueous solution in hand held rubber bulb nebulizer*	OTC
Terbutaline sulfate	Injection/ Tablet	Rx

2.3 Availability of Proposed Active Ingredient in the United States

Epinephrine is a non-selective (alpha and beta$_2$) adrenergic receptor agonist effective as a short-acting bronchodilator. Armstrong previously and solely marketed the CFC-propellant Primatene Mist as an OTC bronchodilator treatment, for a similar indication as proposed here, until December 2011 when the product was required to be removed from the market due to the phase out of ozone-depleting CFC propellants under the Montreal Protocol. The product was not removed from the market for reasons of safety

* Whether hand held rubber bulb nebulizers continue to be appropriate for OTC asthma management was the subject of a Joint Advisory Committee meeting held on February 26, 2014 (see http://www.fda.gov/AdvisoryCommittees/Calendar/ucm380906.htm; accessed March 5, 2014)

or effectiveness. The first epinephrine-containing CFC propellant metered dose inhaler (MDI) was approved by FDA, under the NDA process, in 1967. The original NDA was held by Wyeth Consumer Healthcare.

Epinephrine may also be marketed under a Final Monograph in an aqueous solution administered by a hand held rubber bulb nebulizer. It is available as an Rx-only product under approved NDAs in multiple formulations for various indications taking advantage of its systemic effects on adrenergic receptors resulting in increased heart contractility, vascular smooth muscle contraction and bronchodilation.

2.4 Important Safety Issues with Consideration to Related Drugs

Major U.S. medical associations (American Thoracic Society, American Academy of Allergy, Asthma and Immunology, and American College of Chest Physicians) support the National Asthma Education and Prevention Program (NAEPP), either directly or in principle, in believing that appropriate diagnosis, trigger and symptom management and treatment of asthma require the involvement of healthcare professionals. A good physician-patient relationship helps ensure that asthma sufferers understand their disease, its management and treatment, and how to maximize prevention of the onset and worsening of symptoms. Albuterol and levalbuterol are $beta_2$-selective, short acting adrenergic agonists that have effectively replaced more non-selective agonists such as epinephrine and isoproterenol, for example. See **Section 2.6 Other Relevant Background Information** for details on diagnosis and management of intermittent asthma, and the February 25, 2014 Advisory Committee meeting's briefing material (http://www.fda.gov/AdvisoryCommittees/Calendar/ucm380886.htm) for further safety discussion and references to additional discussion.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This is the applicant's second submission of an NDA for epinephrine inhalation aerosol. The first submission, in April 2013 (NDA 205496) was not filed, most significantly because the submitted electronic document was not adequately formatted to allow substantive review as per 21 CFR 314.101(d). Prior to the April submission, the applicant met with FDA several times to discuss the content of an NDA. FDA stressed the importance of data indicating that the product was safe to use from a cardiovascular standpoint (see **Section 4.4.2 Pharmacodynamics**) as well as data showing that the product can be used and maintained properly and reliably.

Table 3: Sequential Correspondence with FDA

No.	Document type	Contents	Date
1	Meeting Minutes	Meeting Minutes for March 27, 2007 Pre-IND meeting	04/24/2007
2	Response to meeting package questions	Response to questions contained within meeting package dated October 7, 2008	11/25/2008
3	IND Acknowledgement	Acknowledgement of submission dated October 26, 2009	11/04/2009
4	Advice/ Information Request	Advice for protocol E004-A and comments regarding the development program as a whole	11/23/2009
5	Preliminary FDA Responses	Preliminary responses and comments in preparation for October 29, 2010 meeting	10/28/2010
6	Meeting Minutes	Meeting Minutes for October 29, 2010 meeting	11/23/2010
7	Advice	Comments regarding Phase 3 drug development based on E004-A2 and E004-B3 results	05/10/2011
8	Advice/ Information Request	Request pertaining to CFC phase out	06/22/2011
9	Meeting Request Granted	Meeting schedule for September 23, 2011	07/28/2011
10	Preliminary FDA Responses	Preliminary responses and comments in preparation for September 23, 2011 meeting	09/22/2011
11	Meeting Minutes	Meeting Minutes for September 23, 2011 Type B Meeting	10/21/2011
12	Meeting Request Granted	Meeting schedule for January 31.2013	12/10/2012
13	Preliminary Response for Pre-NDA Meeting – Type B	Agency Clarification and Instructions for Data to be submitted for the OTC NDA	01/30/2013
14	Pre-NDA Meeting – Type B	Meeting Minutes for January 31, 2013	01/31/2013

Source: Applicant's submission, Module 2, Section 2.2, p. 4, "FDA Correspondence List"

Important results of the correspondence between FDA and the applicant include:

- Agreement that the 125 mcg dosage strength to provide either 125 mcg (1 puff) or 250 mcg (2 puffs) appeared most appropriate, although the higher systemic bioavailability of epinephrine at those doses, compared to Primatene Mist, required support for safety from the Phase 3 development program.
    - FDA requested a minimum of six months of safety data in an adequate number of test subjects (approx. 300).
- FDA recommended a large and comprehensive consumer behavior program to ensure that consumers understand the label and can follow the directions for cleaning, priming, re-priming and actuation.
- FDA expressed concerns with the applicant's proposal to initially market the product for adults over age 18. The applicant indicated that it had data supporting use by children as young as 12 and partial data in children as young as four years of age. FDA's concerns were based on the prior availability of Primatene Mist for children as young as 4 and the risk that familiarity with that product by former users would lead to off label use. FDA requested all available pediatric data be submitted with the NDA regardless the proposed target population for marketing.
- FDA recommended collecting data on both "malfunctioning" devices (according to subjects) and working devices at the end of their lifespan to determine, by *in vitro* testing, if they were working as intended. FDA asked the firm to conduct label

comprehension and behavioral (human factors) testing to determine understanding of established priming, re-priming, use and cleaning instructions based on the design of the device and dose indicator. FDA stressed that the device must be robust and reliable. The proposed product was considered to be significantly different in formulation and design from the Primatene Mist product to warrant such testing.

- FDA requested performance data to elucidate the potential impact of various in-use conditions on reliability, e.g., how not cleaning the product affects using it as directed.

Reviewer's comments: The results of adherence to these advisements and recommendations are addressed in other reviews.

2.6 Other Relevant Background Information

FDA considered the report of the National Asthma Education and Prevention Program (NAEPP)[1] of the National Heart, Lung and Blood Institute (NHLBI) within the National Institutes of Health (NIH) regarding diagnosis of intermittent asthma and management of related symptoms:

- Asthma is diagnosed if episodic symptoms (e.g., dyspnea [difficulty breathing], wheezing, chest tightness, coughing) of airflow obstruction are present, the obstruction is at least partially reversible, and alternative diagnoses have been excluded.
- Severity of asthma reflects clinical manifestations and can be classified as intermittent, mild persistent, moderate persistent and severe persistent.
- Intermittent asthma in adults and children $\geq$ 12 years of age is classified as the presence of symptoms and use of short-acting $beta_2$-agonists ≤ 2 days per week, nighttime awakening ≤ 2 times per month, no change in normal activities and use of oral corticosteroids no more than once per year for exacerbations.
  - Recognizable symptoms of mild exacerbations are activity-related dyspnea including tachypnea
    - Peak Expiratory Flow 70-80% predicted or personal best, performed by capable persons, indicates a mild exacerbation
    - Symptoms may be managed at home and should improve rapidly with inhaled short-acting beta agonists with the possible addition of a short course of oral corticosteroids
  - Persons with intermittent severity may still have mild, moderate or severe exacerbations
  - Persons with ≥ 2 exacerbations per year cannot have intermittent disease regardless of the frequency or severity of other symptoms
- Ongoing monitoring (medical history and physical exam, pulmonary function testing, quality of life status, etc.) and periodic assessment by a healthcare professional are important

- Written action plans based on signs and symptoms, including peak flow monitoring are recommended for patients with moderate or worse severity disease, or those with history of severe exacerbations

o Asthma pharmacotherapy should be used in conjunction with education to maximize awareness and avoidance of environmental triggers

- Treatment of mild exacerbations should include *only* short-acting beta-agonists as needed
- Inhaled epinephrine is not recommended as a quick-relief medication due to potential for excessive cardiac stimulation, especially in high doses

*Reviewer's comments: The Advisory Committees (**Section 9.3 Advisory Committee Meeting**) considered the NAEPP guidelines as they apply to the proposed product for OTC use. This reviewer addresses some of the committees' concerns there and elsewhere in this review.*

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the quality of the electronic submission was adequate. It was reasonably well-organized with working hyperlinks for ease of review. Regarding the postmarketing safety data, the focus of this review, I requested additional analysis of FAERS data, including that submitted with the 120-day safety update (21 CFR 314.50(d)(5)(vi)(b)). Data were submitted in a timely manner (**Section 8 Postmarket Experience**).

3.2 Compliance with Good Clinical Practices

See the Office of Clinical Pharmacology (OCP) and DPARP reviews for details of the pharmacokinetics and efficacy trials conducted to support the application. The Office of Scientific Investigations was consulted to inspect two sites involved in efficacy trial API-E004-CL-C, sites 18 and 20. These sites demonstrated larger treatment effects compared to other sites and enrolled an average, or greater than average number of subjects. The inspections did not identify any significant observations and no FDA form 483s were issued. The data from these sites are considered acceptable.

3.3 Financial Disclosures

Financial certifications related to the conducted clinical studies supporting this application indicate that no clinical investigators participated in any financial arrangement with the applicant. Certifications may be more fully addressed by clinical

and statistical reviewers from the OCP and DPARP. This reviewer did not primarily evaluate data from new clinical trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

The Office of New Drugs Quality Assurance (ONDQA) team has not yet finalized its review. The drug product includes a 14 mL aluminum canister housing the drug and fitted with a 50 microliter aluminum metering valve and 160-count top-mount dose indicator. The product does not contain an overage above the dose indicator maximum. The formulation contains epinephrine in suspension in HFA propellant with ethanol, thymol and polysorbate 80 (see **Table 4**). The epinephrine ingredient (b) (4) The applicant requests a 24-month expiry based on evaluation of stability data.

Table 4: Chemical Components of Epinephrine HFA

Chemical Material	Used As	Composition (%w/w)
Epinephrine (b) (4)	Active ingredient	(b) (4)
Polysorbate 80, NF	(b) (4)	
Dehydrated alcohol USP		1.0000
(b) (4) (HFA-134a)	Propellant	(b) (4)
Thymol, NF	(b) (4)	

Source: Applicant's submission, Module 2, Section 2.3.P – Drug Product, Table 2.3.P-1, p. 17.

Reviewer's comments: A Warning Letter for manufacturing violations was issued to (b) (4) the manufacturer of the drug substance, epinephrine, in (b) (4) A repeat facility inspection was due in early (b) (4)

The dose indicator is added onto the canister and not integrated into the device as recommended by FDA (see *Guidance for Industry – Integration of Dose-counting Mechanisms into MDI Drug Products*). The indicator also differs from a dose counter as the count is displayed in decrements of 20 with a red bar appearing when 20 doses remain to warn consumers that the canister is nearing empty.

The applicant reports testing functionality and reliability of the MDI and dose indicator performance under routine use and cleaning in the phase 3 clinical trials (Trials C, C2 and D). FDA reviewers from ONDQA and DPARP may address several potential CMC-related issues in their reviews and may recommend labeling changes to address these issues. Reviewers noted device and dose indicator malfunctions reported more frequently than is usual for marketed MDIs (see their reviews and FDA Briefing

Information for Joint Advisory Committees' Meeting
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/ucm380890.htm). Also see **Section 9.3 Advisory Committee Meeting**. Some malfunctions of the device could be due to user error, e.g., clogging due to improper cleaning, or not dispensing because user does not press the actuator properly. Such issues may be addressed by ensuring that "worst case" scenarios are considered by the applicant as it focuses and clarifies the key related instructional and care material in labeling. However, issues with the dose indicator performance are also troublesome. An indicator that overcounts is undesirable because consumers are likely to discard a product that still contains medication. One that undercounts may result in serious untoward consequences with consumers erroneously believing that the product contains medication, and dispensing either an insufficient dose or no dose in a potentially precarious medical situation such as acute bronchospasm.

Reviewer's comment: We strongly consider whether approval and marketing of an MDI drug product is appropriate, regardless whether it is for OTC or Rx use only, if there exists any potential for malfunction when a product is intended, like epinephrine HFA, as a quick-relief product for acute treatment of asthma symptoms. See the DPARP, ONDQA and social science reviews for more discussion regarding the concern over potential design flaws, user error, and whether the product may be relied upon, and the labeling adequately understood, to ensure safe and proper use.

Following the Advisory Committee meeting, the applicant submitted a letter on March 2, 2014 refuting the FDA's analysis of data and requesting an investigation into the "gross distortion of Sponsor's data" addressing the device evaluation. It believes that FDA's analysis and presentation were faulty for the following reasons:

- *The device and dose indicator are FDA approved, "exceptionally robust," and have been commercially available for several years.*
- *FDA focused an inordinate segment of its presentations to device concerns with lesser emphasis in the briefing material, thus limiting the applicant's capacity to offer a retort at the meeting.*
- *FDA's device performance evaluation was "erroneously" perceived as a safety concern and negatively influenced the panelists' votes.*
- *False data were presented, thereby creating "misimpression" of serious safety concerns.*

In a letter from March 20, 2014, FDA responded to the applicant that it was evaluating the issues.

4.2 Microbiology

Dr. Bryan Riley of the Microbiology Staff in the Office of Pharmaceutical Science found the Microbial Limits specification for the drug product acceptable, recommending approval from a product quality standpoint.

4.3 Preclinical Pharmacology/Toxicology

The nonclinical review was not finalized at the time of this review. The reviewer, Dr. Wafa Harrouk, has indicated that there are novel excipients in the product that may not have extensive data available to support human exposure by the inhalation route. Epinephrine was previously approved as the active ingredient in Primatene Mist and there are no outstanding nonclinical concerns regarding the drug substance. Of note, the lethal dose at 50% (LD_{50}) is equivalent to 12 mg/m^2 which is 27 times greater than the maximum recommended daily subcutaneous or intramuscular doses. Plasma concentrations in rabbits, by these routes of administration, result in 44% and 28% greater C_{max} and AUC, respectively, than concentrations following inhalation of epinephrine. Epinephrine is a Pregnancy Category C drug based on nonclinical studies and should be used in pregnancy only if the benefit justifies any potential fetal risk. There are no data on fertility, carcinogenicity or mutagenicity effects, but the ingredient had been available for several decades without clear related untoward consequences.

The applicant states that all excipients are commonly used in pharmaceutical drug products. It reports that HFAs in MDIs are not carcinogenic, mutagenic or biologically reactive and do not accumulate in tissues, usually being exhaled intact almost immediately after inhalation. Gene toxicology, reproductive, acute, subchronic and chronic inhalation, toxicokinetic, cardiac sensitization, and carcinogenicity studies were all conducted to support safety of HFAs.

4.4 Clinical Pharmacology

See **Table 7** for a list of trials, including the clinical pharmacology evaluation, conducted to support this NDA. The clinical pharmacology review and recommendation of 'acceptable' was finalized on April 9, 2014. Summary details are provided in the briefing material supporting the Advisory Committees' meeting on February 25, 2014. Two dose-ranging and three PK trials were conducted. Systemic epinephrine exposure at the therapeutic dose is difficult to detect; therefore, investigated doses were 6 fold higher so that plasma concentrations could be reliably quantified. Concentrations were undetectable within one hour post-dose.

4.4.1 Mechanism of Action[2]

Epinephrine is a catecholamine that can be administered by a variety of routes, e.g., injection, subcutaneous and inhalation. The drug is a potent, non-selective alpha- and beta-adrenergic receptor agonist. The degree of stimulation depends on the dose and route of administration. The results of stimulation are arteriolar vasoconstriction ($alpha_1$) or vasodilation ($beta_2$), increased chronotropic and inotropic cardiac response, bronchial smooth muscle relaxation ($beta_2$) and increased glycogenolysis (risk for hyperglycemia). Hypokalemia may occur as potassium is taken up by cells in skeletal muscle.

The drug is widely distributed, but does not cross the blood-brain barrier to great extent. The drug's activity rapidly terminates upon metabolism to inactive products further undergoing sulfation or glucuronidation and excretion in urine. Upon inhalation, the drug is only minimally absorbed, having its effect primarily on beta receptors in the respiratory tract within 1-5 minutes.

4.4.2 Pharmacodynamics

Pharmacodynamic (PD) assessment of epinephrine HFA included a focus on cardiovascular findings in clinical trials, particularly after high dose exposure. Reviewers from the Division of Cardiovascular and Renal Products (DCRP) offered a consult review on December 5, 2013 to provide an update on the cardiac safety of epinephrine HFA at the proposed dose. DNCE had asked them to review the safety database from conducted clinical trials and postmarketing experience and comment on the cardiac safety if the drug were approved for OTC marketing. As noted in **Section 4.4.3 Pharmacokinetics** the bioavailability of the drug in the HFA product is greater than that administered in the previously marketed CFC-containing product. Overall, DCRP considered the data generally complete and reassuring at the proposed dose.

The Division had consulted previously in December 2011 and January 2013. In those consults, DCRP noted that the C_{max} determined in clinical pharmacokinetics testing (Trials B, B2 and B3) was 2.6-4.5 fold higher with the HFA product vs. CFC product in identical dose regimens (up to 10 actuations). The greatest concentration differences (up to 4.5 fold) appeared to be most accurate because measurements in that trial, B2, were made in closer approximation to T_{max} ~ 2-3 minutes. Other trials quantified serum levels at five minutes, beyond T_{max}. Notably, the serum levels were venous, although arterial blood would have been a more accurate source for an inhaled drug such as epinephrine HFA. Hence, the measured levels are likely lower than actual. Regardless, the drug is rapidly metabolized and undetectable by 60 minutes post-dose.

2 Epinephrine drug monograph (clinical pharmacology online, http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=223&aprid=18010; accessed April 1, 2014)

The applicant had been advised to provide data on maximal increases in heart rate, patient characteristics of those with clinically significant increases (> 20 bpm), and ECG-documented arrhythmias. Prior to NDA submission, FDA requested detailed analysis of AEs that may correlate events such as chest pain and tachycardia with changes in BP and HR as well as those AEs leading to discontinuation from trials. Adequate characterization of the effect of epinephrine HFA on BP, HR and serum potassium in a diverse population are also important to capture the overall cardiac safety of a more bioavailable inhaled epinephrine drug product compared to the previously marketed CFC-containing product. See the other clinical reviews.

While the applicant offered literature support comparing epinephrine levels after moderate exercise with levels obtained in its trials, post-exercise physiologic levels were still lower than results from trial B2. Yet, several pharmacodynamic safety measures indicated that the resultant drug levels were not likely associated with significant safety issues, i.e., transient hyperglycemia, hypokalemia, increases in blood pressure (BP) or heart rate (HR), or arrhythmias. The measurements were made at 15-30 minutes post-dose, well beyond the 2-3 minute T_{max}, and were provided as means, where assessment of individual variability, particularly for BP and HR, is not possible. However, the dose strengths were up to a maximum of over 6 times higher than the to-be-marketed product (1600 mcg vs. 250 mcg) and no significant PD changes or trends were noted overall, even at the highest serum drug levels.

The Division conducted a data mining search of the highest magnitude scores as indicated by Empirical Bayes Geometric Means (EBGM) for AEs reported in FAERS with use of the CFC-containing Primatene product. This method identifies drug-AE combinations that are observed and reported more frequently than expected. The EBGM value is indicative of the strength of the relationship between use of a drug and the AE reported. The highest cardiac-related scores above an arbitrary minimum threshold of 2 were palpitations (3.1), chest pain (2.7) and heart rate increased (2.5). Scores at two or above signify an AE reported at least twice as often as expected. No serious cardiac AEs rose to levels above two. Scores for drug abuse and dependence were also relatively high indicating that risk for overuse and misuse must be considered (see **Section 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**). Similarly, clinical trial data demonstrated some potential cardiac AEs reported in higher frequencies by subjects taking repeat doses of the test drug (see **Table 5**). Such AEs were not reported in the single dose trials. None of the AEs were serious or severe in intensity.

Table 5: Patients with Potential Cardiac AEs in the Repeat Dose Clinical Trials

	Study C						Study C2					
	E004		Primatene		placebo		E004		Primatene		placebo	
# treated:	248		64		61		134		35		38	
adverse event	n	%	n	%	n	%	n	%	n	%	n	%
chest pain/discomfort	6	2.4%	1	1.6%	0	0.0%	3	2.2%	0	0.0%	1	2.6%
hypertension/BP elevated	0	0.0%	2	3.2%	0	0.0%	2	1.5%	0	0.0%	1	2.6%
tachycardia	1	0.4%	0	0.0%	0	0.0%	1	0.7%	0	0.0%	0	0.0%
palpitations	2	0.8%	1	1.6%	0	0.0%	1	0.7%	0	0.0%	0	0.0%

n = number of patients with at least one event, not number of events
Source: Table 2, p. 4; Dr. Thomas Marciniak's (DCRP) consult review (DARRTS; December 5, 2013)

Based on the overall findings summarized above and described in more detail in the DPARP and clinical pharmacology reviews, the PD safety assessment (BP, HR, potassium) was reassuring, particularly for those who are likely to use the product as directed and those without underlying cardiac disease. However, if approved, use of the product may result in clinically significant increases in BP and HR following overdose or other misuse. These concerns are addressed elsewhere in this review.

Reviewer's comment: Adequate data were provided to make the assessment that cardiovascular safety appears to be supported when the product is used at the proposed dose and regimen.

4.4.3 Pharmacokinetics

In trial B, two dose strengths of epinephrine HFA (125 mcg and 160 mcg/inhalation) were compared to Primatene Mist (220 mcg/inhalation). The AUC of total epinephrine (exogenous + endogenous) was 10% higher after an epinephrine HFA 125 mcg dose compared to a Primatene Mist 220 mcg dose. C_{max} of total epinephrine was also approximately 2.5 times higher for epinephrine HFA at 125 mcg. T_{max} was observed at five minutes post dose, the initial serum collection. At FDA's request, trial B3 was conducted to evaluate lower dose strengths of epinephrine HFA (90 and 100 mcg/inhalation) compared to Primatene Mist. This request was made due to the higher than expected systemic exposure of epinephrine at 125 mcg/inhalation from epinephrine HFA compared to 220 mcg of Primatene Mist in trial B (Trial B2 was ongoing at the time). The C_{max} was observed two minutes post-dose, but total epinephrine was still 2.4 times higher with 90 mcg/inhalation (12 inhalations) compared to Primatene Mist dosing, although AUC for epinephrine HFA was nearly 8% lower. Trial B2 offered the most comparable results because the first serum collection was conducted closest to the true T_{max}, two minutes post dose. In this trial, the C_{max} of total epinephrine was 4.5 times higher (860 vs. 190 pg/mL) for epinephrine HFA than Primatene Mist. AUC was 37% (8500 vs. 6190 pg/mL*min) higher than with Primatene Mist (see **Table 6**).

Reviewer's comments: Above, ***Section 4.4.2 Pharmacodynamics*** *includes discussion of cardiovascular safety with higher systemic exposure following use of the proposed epinephrine HFA. In her review, Dr. Pippins also addresses safety with higher comparative epinephrine exposure.*

Table 6: Mean AUC and C_{max} for Epinephrine HFA and Primatene Mist, PK Trials B and B2

	Epinephrine HFA		Primatene Mist	
Trial	**B**	**B2**	**B**	**B2**
N	24	23	22	23
Dose (mcg)	10x125 mcg/inh	10x125 mcg/inh	10x220 mcg/inh	10x220 mcg/inh
$AUC_{0\text{-}6hr}$ (pg/mL*min)	7938	8500	7218	6190
C_{max} (pg/mL)	340	860	139	190

Source: Adapted from Applicant's submission, Section 5.3.3.1, Report-study-b, Table 7-4, p 71 and Report-study-b2, Table 7-5, p. 75 (Table 2, Clinical Review for February 25, 2014 Advisory Committees' Meeting, Briefing Material, p. 50).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 7: Overall Clinical Trial Plan for NDA 205920

Items	Efficacy, Dose Range and Safety		PK / High Dose Safety			Long-term Efficacy/Safety		Pediatric Long-term Efficacy/ Safety
Study ID	**E004-A**	**E004-A2**	**E004-B**	**E004-B2**	**E004-B3**	**E004-C**	**E004-C2**	**E004-D**
# of Subjects	26	30	24	23	23	373	207*	70
E004 Dose Range, mcg	250, 320, 440	90, 125, 180, 200, 250	1250, 1600	1250	1080, 1200	2×125, QID		2×125, QID
Study Phase	I	II	II			III		III
Type of Subjects	Asthma Patients		Healthy Volunteers			Adult/Adolescent Asthma Patients		Pediatric Asthma Patients
Dosing	Single dose, 2 Inhalations		Single high dose, 10-12 Inhalations			Multiple dose, 2 Inhalations, QID		Multiple dose, 2 Inhalations, QID
Treatment Duration	3- 5 Treatments		1 Treatment at High Dose			12 weeks	Additional 3 Months	4 weeks
Major Safety Evaluations	Initial Safety		High Dose Safety			Adult 12-Week Safety	Adult 6-Month Safety	Pediatric Safety
Type of Study	Double-blinded or Evaluator-blinded		Evaluator-blinded			Double-blinded or Evaluator-blinded		Double-blinded
	Crossover		Crossover			Parallel		Parallel
Type of Controls	Placebo and Active Control (Primatene®)		Active Control (Primatene®)			Placebo and Active Control (Primatene®)		Placebo Control

* Patients for Study E004-C2 were enrolled from those patients who completed Study E004-C.
Source: Applicant's submission; Module 2, Summary of Clinical Safety, Section 2.7.4.1.1; Table 2.7.4 – 1, p. 12

5.2 Review Strategy

The clinical portions of this NDA will undergo review by several reviewers. This reviewer will focus on postmarketing safety of the Primatene Mist product marketed until the end of 2011. Reviewers from DPARP, OB and clinical pharmacology will evaluate the phase 2 and 3 clinical trials (A, A2, B, B2, B3, C, C2, D). Based on data submitted in the application and with input from the Advisory Committees' Meeting, reviewers will

offer recommendations as to whether epinephrine HFA is safe and effective for OTC use.

In January 2014, this reviewer requested more detailed postmarketing safety data, specifically full line listings of Adverse Events from the FAERS database. I asked for the data grouped as Preferred Terms (PTs) under the System Organ Classes (SOCs) and further stratified by seriousness and age (< 4 years; 4-11 years; 12-64 years; >64 years and unreported). The applicant submitted data on January 27, 2014.

5.3 Discussion of Individual Studies/Clinical Trials

Not applicable.

6 Review of Efficacy

Efficacy Summary

As stated above, the efficacy trials submitted to support approval will be reviewed by DPARP and OB reviewers. Dr. Pippins' review and recommendation of 'complete response' from a clinical perspective was finalized on April 14, 2014. She stated that the clinical investigations provided sufficient evidence that the product was efficacious as a bronchodilator. However, her review identified "sufficiently concerning" questions about the "device robustness and reliability." She noted that her recommendation is preliminary pending the review and recommendation of reviewers in ONDQA. From the statistical standpoint, Ms. Zhao found "statistical evidence of a difference between E004 [epinephrine HFA] and placebo in asthma patients aged 12 years and older…" Her review was finalized on March 6, 2014.

Two phase 2, single-dose, dose-ranging (E004-A, E004-A2) and three phase 3 safety and efficacy trials (E004-C, E004-C2, E004-D) were conducted to support the applicant's epinephrine HFA for relief of mild symptoms of intermittent asthma in the OTC setting. The objectives of the pivotal efficacy trial (Trial C) were to both compare the proposed product (epinephrine HFA) to a placebo HFA-propellant Metered Dose Inhaler (MDI) and the previously marketed Primatene Mist CFC-propellant MDI, and to assess functionality, reliability and performance of the device. Trial C2 was a three month safety extension trial in 207 subjects who completed Trial C, for a total of 24 weeks' participation. Another safety and efficacy trial, E004-D, was conducted in children 4-11 years of age, but the applicant is not seeking approval for use of its product in children under 12 (see **Section 7.6.3 Pediatrics and Assessment of Effects on Growth**). In total, 443 subjects were enrolled in Trials C, C2 and D with exposure to test products for up to 24 weeks. Trial C included 21 pediatric subjects, 12-16 years of age. Trial C2 enrolled 12 from the same age group.

Endpoints:

- Primary: Area Under the Curve (AUC) of post-dose Forced Expiratory Volume in one second (FEV1) percentage change from same day baseline versus time (AUC of ∆% FEV1)
    - Compare analysis AUC of ∆% FEV1 for Treatment arm (epinephrine HFA) and placebo arm at visit 5 (week 12)
- Secondary endpoints include the time curve of ∆% FEV1, AUC_{0-t} of ∆FEV1, t_{onset}, F_{max}, t_{max}, duration, ∆%FEV1(t_i) and responder rate (R%)
- Self-recorded parameters include Daily Asthma symptom Scores (DASS), mean Nighttime Awakening Scores (NAS) and mean daily morning pre-dose Peak Expiratory Flow Rate (PEF)

Reviewer comments: In the Filing Communication of October 4, 2013, FDA requested analyses of mean FEV1 data over time. FDA had previously requested these data in addition to AUC of ∆% FEV1 at a meeting on January 31, 2013, prior to submission of the application. Such data better assesses the treatment effect.

7 Review of Safety

Safety Summary

Safety data from completed clinical trials will be evaluated by reviewers from DPARP. A brief, additional summary of cardiovascular safety from completed, high dose PK trials (E004-B and B2) is found in **Section 4.4.2 Pharmacodynamics** and in a consult review from DCRP. Several pharmacodynamic safety measures indicated that resultant drug levels at doses nearly 13 fold higher than proposed (125 mcg versus 1600 mcg in Trial B) were not likely associated with significant safety issues, i.e., transient hyperglycemia, hypokalemia, increases in BP or HR, or arrhythmias. There were no data identifying a cardiovascular safety concern when the product was used as intended, according to labeling.

The applicant submitted postmarketing data (**Section 8 Postmarket Experience**) supporting the safety of Primatene Mist, a predicate OTC MDI approved for relief of mild asthma symptoms. The applicant believes the safety experience is relevant to future experience of epinephrine HFA if approved. The adverse event (AE) data resulted from marketing experience from 1997-2012 reported to both the applicant's and Primatene Mist's former manufacturer's (Wyeth) pharmacovigilance databases and FDA-Adverse Event Reporting System (FAERS). This reviewer also evaluated data from the American Association of Poison Control Centers and published literature. Overall, the total relative number of AEs compared to the millions of units distributed (18.5 million units, 2008-2011) over the evaluation period was small. Serious AEs, including deaths, accounted for approximately three quarters of all the events. I reviewed the narratives of all serious cases submitted by the applicant and many cases in FAERS, in addition to conducting focused searches of FAERS to identify potential safety signals. For example, I searched for serious reports of "ineffectiveness" which may actually describe

inappropriate use for more than mild asthma exacerbations without the expected result, adequate relief of bronchospasm. I also searched for cases of overuse and misuse (**Section 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**) to ascertain whether consumers are likely to administer more than the directed number of doses, or administer doses more frequently than directed to either achieve the expected effect or abuse the product. Overall, the data, including cardiovascular data, were supportive of safety of an epinephrine inhalation aerosol available in the OTC setting.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

Epinephrine is a Pregnancy Category C drug and applicable warnings should remain on labeling.

7.6.3 Pediatrics and Assessment of Effects on Growth

The previously marketed OTC Primatene Mist product was labeled for use by adults and children as young as four years of age for a similar indication as proposed in this application. The applicant proposes initial labeling of this new epinephrine HFA for use by adults and children as young as 12 years of age. For children 4-11 years of age, the applicant has so far completed one 4-week efficacy trial, API-E004-CL-D. It submitted the final report for this trial, but, at this time, is not seeking a claim for use of the product by children as young as four. Ms. Zhou's statistical review (DARRTS, March 6, 2014) indicates that the data do not adequately support efficacy in children 4-11 years of age. Another efficacy trial (API-E004-CL-D2) in the same age group was ongoing at the time of submission of the NDA. Based on exploratory findings in Trial D, trial D2 was modified by the applicant to evaluate efficacy of only a single dose. (b) (4)

(b) (4)

Notably, Primatene Mist was not approved for use by children under age four due to safety concerns. The applicant seeks a partial waiver consistent with FDA's prior determination that the product is not appropriate for children under age 4.

*Reviewer's comments: This reviewer is concerned about approval of the proposed product with a limitation to the target population of a similar drug that had previously been available to a wider population of young consumers (< 12 years). In addition, the Advisory Committees believed that there were limited data supporting use by consumers 12 to 18 years of age. There were only 21 subjects under age 17 enrolled in the pivotal clinical trial (Trial C). See the DPARP and OB reviews. It is likely that young consumers, and their parents, will choose to use or administer the product as they may have historically when it was previously available in the CFC formulation. While the postmarketing data for Primatene Mist (**Section 8 Postmarket Experience**) and the high dose PK evaluation in adults (**Section 4.4.2 Pharmacodynamics**) do not identify safety signals, the greater bioavailability of epinephrine in the proposed product raises the possibility of safety concerns particularly with overuse by children.*

A PeRC meeting will be held on April 30, 2014 to discuss the applicant's deferral and waiver requests and to discuss whether the proposed product may be safe and appropriate for children over 12 years of age. The Pediatric and Maternal Health Staff were consulted to provide expert opinion based on prior related consult reviews and formal review of this NDA. It completed its review on March 14, 2014. Dr. Ethan Hausman reiterated that national guidelines by the NAEPP do not recommend use of epinephrine for treatment of asthma symptoms in any age groups due to concerns for cardiac overstimulation. If epinephrine HFA is approved, PMHS recommended contraindicating the product for children less than 12 years of age until adequate pediatric safety and efficacy data are established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Reports of drug abuse and drug dependence were not infrequent with use of Primatene Mist, even in light of the few AEs reported overall. They are of concern when considering potential for cardiovascular AEs with overuse and misuse. This reviewer identified 46 reports (serious reports; N=40; 4 deaths) captured under the established "Drug Abuse and Drug Dependence" Standardized MedDRA Query (SMQ). SMQs are related groupings of Medical Dictionary for Regulatory Activities (MedDRA) PTs that are associated with the Query topic. The SMQ includes a range of Preferred Terms (PT) reflecting potential drug abuse, dependence, intentional and accidental misuse or overdose, drug diversion, toxicity and complications from abuse. The possibly drug-relatable deaths include:

- (b) (6) – A woman reported that her brother died of respiratory failure reportedly caused by excessive use of and addiction to the product
- (b) (6) – A consumer relayed (b) (6) the death of a child following overdose of Primatene® Mist used to "get high"
- (b) (6) – Intentional overdose and misuse was reported for a 66 year old in the (b) (6) Annual Report of the American Association of Poison Control Centers

Many cases indicated that users considered themselves dependent on the product, i.e., they "needed" to use the product multiple times daily, or they overused the product to treat their symptoms, e.g., administered more puffs daily than directed. Some stated that symptoms were not always due to asthma, nor did consumers always have a prior asthma diagnosis (Primatene Mist was contraindicated for use without a known asthma diagnosis). Potentially pertinent cases related to the safety of the drug in the OTC setting:

- A 51 year old consumer experienced palpitations while using Primatene® Mist and Primatene® tablets (ephedrine and guaifenesin) simultaneously as needed for her 20-year history of "asthma." She had a Holter monitor placed and her physician expressed concern about overdose.
- A 44 year old asthmatic reported administering 18 puffs of Primatene® Mist daily for two years (label directed users to see a doctor if they needed 12 puffs maximum per day and more than nine daily puffs in any three week period). The consumer also used salbutamol, theophylline, fluticasone propionate and ipratropium bromide for asthma control and management. He reported chest and arm pain with irregular heart beat while using Primatene. He reported being "addicted" to the product.
- A consumer reported 10 years' use of the product with up to one puff every 15 minutes for asthma. She described being "addicted," that her "lungs will 'cease up' and her lips will turn blue" if not using the drug.

This reviewer performed a data mining search using Empirica™ Signal (Version 7) to ascertain the magnitude of drug abuse, dependence and overdose AEs. The following PTs had EB05 > 2:

- Drug abuser (EB05 = 30.7)
- Drug dependence (EB05 = 7.8)
- Drug screen positive (EB05 = 3.5)
- Overdose (EB05 = 2.8)

Reviewer's comments: The greatest potential consequences of overuse/misuse of epinephrine HFA are cardiovascular effects. While there was no preponderance of cardiovascular AEs with overuse, it appears from these reports that consumers may still overly rely on the product to manage all kinds of respiratory symptoms. This raises concerns for safe and proper use of a drug for "OTC," i.e., self-diagnosable and self-manageable, conditions. Asthma related bronchospasm and symptom management would likely be improved by regular care of a physician and use of controller-type medications (e.g., inhaled corticosteroids) rather than OTC "rescue" drugs that risk being used improperly, unduly delaying appropriate respiratory care, and suffering more serious outcomes.

8 Postmarket Experience

Applicant's Pharmacovigilance Database

There may be substantial overlap in data from postmarketing sources. For example, the FAERS database includes most U.S. cases initially reported directly to an NDA holder and maintained in the firm's pharmacovigilance database. The FAERS database contains spontaneous reports of AEs from a variety of sources. Interpretation of spontaneously reported AEs has several limitations:

- Reports are submitted voluntarily and the magnitude of underreporting is unknown.
- The reporting systems yield reporting rates, and not incidences.
- Clinical information is often limited in the reports, and causality cannot often be determined.
- Duplicate cases are common, may not be removed, and may affect the impact of any further analysis.
- Reporting may be biased. A reporter's intent may confound the interpretation of associations between use of a drug and AEs. For example, a lawsuit or a publication may stimulate reporting.

A causal relationship between the use of epinephrine inhalers, particularly Primatene Mist, and any particular AE or clustering of AEs is difficult to determine. An event may occur due to a consumer's underlying disease, past medical history, concomitant medications or may be only coincidental in its temporal relationship to use of the drug. Below, we report on the cases included in each individual database.

For use of the CFC-containing Primatene product, the applicant submitted reports of AEs from its pharmacovigilance database for the years 2008-2012 as previously discussed with FDA. In total, there are only 110 unique reports that include 179 AEs. Forty eight (N=48; 26.8%) AEs were serious (26 case reports). Three deaths were reported. The applicant reports a total of 18.5 million units distributed over the same time period. From 2008 through 2011 (the last year of marketing), distribution averaged 4.6 million units per year.

The most frequently reported (>5%) System Organ Classes (SOC) were:

- General Disorders and Administrative Site Conditions (N=70; 39%)
- Respiratory, Thoracic and Mediastinal Disorders (N=39; 21.8%)
- Gastrointestinal Disorders (N=22; 12.3%)
- Cardiac Disorders (N=14; 7.8%)
- Nervous System Disorders (N=10; 5.6%)
- Investigations (N=9; 5%)

The most frequently reported nonserious AEs, by Preferred Term (PT), were:

- Drug ineffective (N=37)
- Product taste abnormal (N= 14)
- Throat irritation (N=13)
- Dyspnea/asthma (N=8)
- Breath alcohol test positive/Drug screen positive (N=7)

- Chest pain/discomfort (N=6)

Other less-frequently reported, nonserious AEs that are possibly drug- and cardiac-related were “tremor,” “palpitations,” “cardiac flutter,” and “heart rate increased.”

The applicant submitted narratives for all 26 serious cases. The most frequently reported SAEs were:

- Dyspnea/asthma (N=5)
- Tachycardia/heart rate increased (N=4)
- Drug dependence (N=4)
- Cardiac arrest/myocardial infarction (N=3)

Representative serious cases (examples of serious overuse and misuse cases are described in **Section 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**) included:

- A male of unknown age with a history of diabetes mellitus and encephalitis was hospitalized after a cardiac arrest while using Primatene® Mist. No additional information was provided. The dosing frequency was unreported.
- A 70 year old male was hospitalized with chest pain and asthma symptoms. He also reportedly suffered a stroke due to a blood clot. The reporter stated that the patient was instructed to stop using Primatene® Mist because it may have led to tachycardia and cardiac-related symptoms (he was also treated with furosemide for congestive heart failure while in the hospital).
- A 61 year old male with a history of asthma took a single puff of Primatene® Mist for an asthma attack and suffered increased heart rate. He was hospitalized for evaluation of myocardial infarction and advised that use of Primatene may have resulted in an “altered rhythm” due to “rapid pulse rate.”

The serious cases reporting presumed “ineffectiveness” (N=7 total*) include:

- A 59 year old female with apparent history of asthma used Primatene® Mist twice daily for a few weeks upon the instruction of her doctor. She was hospitalized due to “lack of effect” and worsening respiratory symptoms.
- A 41 year old female with asthma and a thyroid disorder had used Primatene® Mist for an acute asthma exacerbation. She took two initial puffs for wheezing and cough. Without much improvement she took two more puffs 3-4 hours later. Her symptoms worsened overnight, and she was hospitalized for further treatment. She was instructed to stop using Primatene. She was prescribed albuterol, fluticasone and prednisone with additional asthma education. She stated that her asthma was never previously severe, so she rarely saw a doctor and used only Primatene for exacerbations.

* These serious cases did not all include a “drug ineffective” AE, but the narratives indicated that consumers had serious outcomes because they believed the drug was not effectively treating their symptoms.

- A male of unknown age without reported medical history took several puffs of Primatene® Mist to manage asthma symptoms. With no improvement, he was hospitalized. He was subsequently diagnosed with asthma, atrial fibrillation and atypical pneumonia and prescribed several medications.
- A 58 year old female with history of asthma reported worsening respiratory symptoms after using Primatene® Mist (two puffs a "couple of times a day"). She was seen in an emergency room. She also used Primatene (ephedrine and guaifenesin) and albuterol.
- A 47 year old male with asthma reported no relief after using Primatene® Mist instead of his prescribed asthma medication (fluticasone and salmeterol). He reported suffering a heart attack at the time of his respiratory symptoms.
- A male of unknown age was diagnosed with COPD after using Primatene® Mist for asthma-like symptoms with persistent trouble breathing. Upon hospitalization, the consumer was told the Primatene "masked his symptoms" prolonging his illness.
- A female of unknown age experienced no relief following use of Primatene® Mist for an "asthma attack." She lost consciousness and was transported to a hospital. No further details were available.

Reviewer's comment: Ineffectiveness was the most frequently reported AE (N=37 nonserious AEs). The number of serious cases was small, however, this reviewer is concerned that consumers who report lack of drug effect (ineffectiveness) may actually have either more severe asthma (or may not recognize a more severe exacerbation), an alternative respiratory diagnosis or potentially unrelated disease (e.g., cardiac). Clearly, such consumers should be under the care of a physician, obtain a diagnosis and receive appropriate management and treatment. If they have persistent asthma, they should be treated with an appropriate combination of controller and rescue medications under established asthma action plans. They should have regular follow up with their physicians and be well educated on how to recognize worsening symptoms and what steps to take for appropriate medical management. This generally requires regular interaction with a physician to ensure understanding of the disease process and how to manage it.

The applicant submitted narratives of the three reported deaths:

- 58 year old male had been using Primatene® Mist for three years when he was hospitalized in (b) (6) for a "lung problem." He died one month after hospitalization. No specific details were provided.
- A female of unknown age, "a young girl," reportedly died "years ago" following use of Primatene® Mist.
- A female of unknown age reportedly felt heaviness in her chest and presented to an emergency room. The patient was examined, received a chest X-ray (normal), and was treated with albuterol with some improvement. The reporter, her husband, indicated she was tachycardic with low oxygen saturation (88%). After discharge, she began to worsen and returned to the ER. She died and was found on autopsy to have

"blood clots in the lungs." A "Primatene inhaler" was found in her pocket which she reportedly used only once, prior to the ER visit.

Reviewer's comments: The total number of AEs reported to the applicant is quite small in light of the millions of units distributed over the same time period. There is no clear reason why the reporting rate is so low. However, as noted above, there are many limitations to the interpretation of data reported for drugs under postmarketing surveillance.

Yet, the number of reports are so low that adequate labeling for Primatene Mist and similar labeling for the proposed epinephrine HFA may deter consumers with either more significant asthma, an alternative diagnosis for their symptoms or other reasons to first seek the advice of a physician before use. The proposed label states that consumers must have an asthma diagnosis and use the product for only mild symptoms. A label may also adequately direct consumers who do not benefit from the drug, or whose symptoms worsen, to seek medical advice. Whether such a label is achievable will depend on the overall assessment of the data by all reviewers, including whether the device and dose indicator are reliable enough to allow proper use of the product.

FDA Adverse Event Reporting System (FAERS)

The applicant's search of FAERS identified 389 cases reported with use of Primatene Mist from 1997-2012. The cases included 1174 AEs. Over this same time period, the applicant estimates 66 million units of Primatene were distributed (approx. 4.4 million per year). The most frequently reported AEs (>5%) by SOC were:

- General Disorders and Administration Site Conditions (N=207; 17.6%)
- Respiratory, Thoracic and Mediastinal Disorders (N=196; 16.7%)
- Gastrointestinal Disorders (N=102; 8.7%)
- Psychiatric Disorders (N=101; 8.6%)
- Injury, Poisoning and Procedural Complications (N=94; 8%)
- Nervous System Disorders (N=87; 7.4%)
- Investigations (N=74; 6.3%)
- Cardiac Disorders (N=59; 5%)

The most frequently reported AEs (>2%) by PT were:

- Drug ineffective (N=40; 3.4%)
- Drug Abuser Not Otherwise Specified (N=35; 3%)*
- Dyspnea (N=33; 2.8%)
- Drug Dependence (N=31; 2.6%)
- Asthma (N=24; 2%)

* Upon reviewing FAERS for similar cases, nearly all of the "Drug Abuser" reports were considered 'Null' and canceled because no specific user/patient was identified.

The applicant provided tables with AE data categorized most importantly by gender, age (< 4 years, 4-11 years, 12-64 years, > 64 years), and seriousness. The majority of AE reports were made by or for consumers from 12-64 years of age (N=723; 61.5%). Nearly 30% (N=349) had age unreported, with 8.3% (N=97) >64 years of age and only five AEs (all serious) reported for children < 4 years. There were 341 serious cases reported (87.7% of total), with 1032 SAEs (87.9% of all AEs) including 41 deaths. I reviewed the reports of death. None identified any new safety concerns. Either the information was too limited in detail, or patients had concomitant diagnoses or medication use that confounded assessment of an association between Primatene Mist use and the outcome. The SAEs were identically reported in rank order and similarly distributed by age as were the AEs overall. Additionally, the applicant identified several AEs of "special interest" for specific focus during the conduct of the clinical trials. Those not considered possibly or likely cardiac-related (chest pain or discomfort, tachycardia, heart rate increased, QT_c prolongation), and thus not addressed elsewhere in this review, included only tremor. Reports of tremor (N=2 SAEs) in the postmarketing data did not signal a safety concern. The applicant also separately reported on cardiovascular AEs (N=59; 5%), limiting the relevant PTs to:

- Heart rate increased
- Myocardial infarction
- Blood pressure increased
- Palpitations
- Cardiac arrest
- Hypertension
- Hypotension
- Tachycardia

Among only cardiac-related AEs identified by the applicant, "heart rate increased/ tachycardia" were the most frequently reported overall AEs (32.2%; 19/59) and serious AEs (30.9%; 17/55). However, these AEs accounted for only 1.6% of all AEs, and 1.6% of all SAEs. "Myocardial infarction," "blood pressure increased," and "palpitations" and "cardiac arrest" followed in frequency of reporting. Most consumers with myocardial infarction and cardiac arrest had primary heart disease, and, according to labeling, would have been expected to have sought medical advice prior to use. Twelve deaths included cardiac-related AEs in the reports. None raised a safety concern.

The applicant also provided data comparing rates of AE reporting (overall AEs, SAEs, cardiac-related AEs) from use of Primatene Mist to rates from use of the commonly used Rx-only inhaled bronchodilator, albuterol.

Reviewer's comment: For several reasons, I will not review the comparison data as I do not consider this comparison of AEs relevant to the safe use of epinephrine HFA in the OTC setting:

- *Primatene Mist was indicated only for relief of mild symptoms of asthma, whereas albuterol is an effective, Rx-only "rescue" treatment for all severities of asthma. Albuterol users may have more serious disease, or other significant co-morbidities that could contribute to and confound AE reporting rates.*
- *Albuterol is indicated for bronchodilation due to any cause of bronchospasm with reversible obstructive airway disease, not only asthma-related bronchospasm. This may impact the rate of reporting.*
- *AEs related to use of albuterol inhalers may be reported more frequently because healthcare professionals prescribing the products may, generally, be more aware of the MedWatch reporting process, increasing the rate of reporting.*
- *There are many generic versions of Rx single- and combination-ingredient inhalers containing albuterol, while Primatene Mist was the only available epinephrine inhaler.*
- *Awareness of the phasing out of CFC-containing inhalers may have contributed to the low number of AE reports for Primatene in recent years as consumers discontinued using the product and switched to products like albuterol.*

This reviewer conducted a FAERS search for Primatene Mist under the SMQ "lack of efficacy/effect" and for the related PT "condition aggravated." There were 55 events. Most were forwarded as MedWatch reports by the manufacturer. The reports identified device malfunctions and similar reports as above where ineffectiveness is discussed. Reporters described more serious asthma symptoms, or non-asthma conditions or symptoms that did not benefit from use of Primatene Mist. All of these reports were considered serious. There were only a few hospitalizations and no deaths.

Finally, this reviewer searched FAERS for reports of adverse events in children (< 18 years of age) to ascertain the frequency and seriousness of pediatric reports. Familiarity with Primatene Mist increases the likelihood of use of epinephrine HFA by children younger than 12. We identified 25 reports (seven serious cases) overall. Similar to reports described in adults, ineffectiveness, aggravation of asthma symptoms and mild cardiac-related AEs, e.g., palpitations and chest discomfort, were commonly reported. As expected, most reports contained limited details. There were two deaths:

- (b) (6) – A 10 year old boy seized while in a pool. He suffered cardiorespiratory arrest and died. The reporter, a healthcare provider, stated that an autopsy was non-contributory, but suspected that Primatene Mist, or Primatene tablets, had resulted in an arrhythmia leading to the seizure and arrest.
- (b) (6) - A 17 year old female with past history of minor respiratory complaints had been using Primatene infrequently for chest discomfort and respiratory symptoms. She did not have an asthma diagnosis. An autopsy determined that a severe asthma exacerbation resulting in a sudden cardiac arrhythmia had caused her death. There was no clear evidence that her death was caused by use of Primatene.

AAPCC

I reviewed the Annual Reports for 2008-2012 of the AAPCC-NPDS[3]. The AAPCC receives information collected from telephone conversations at poison control centers nationwide on education or management of product exposures and poisoning. Data are collected for not just drugs, but for over 400,000 types of products including viral or bacterial agents and commercial products and chemicals. All 57 poison centers nationwide upload data automatically to the NPDS, thereby maintaining a continuously updated surveillance system. I searched the Reports for the terms "Primatene" and "epinephrine." Only line listings are provided unless death was the outcome. I found a single listing, in the 2010 report, resulting in death. The narrative described a 28 year old female who administered 30 doses of her epinephrine inhaler. The report presumes use was for bronchospasm. She had two subsequent seizures without a known history. A physical exam included BP 111/82 and HR 100-130s. An EKG showed sinus tachycardia with a prolonged QTc of 508 msec (normal < 440 msec). Brain imaging showed basilar artery occlusion and a large ischemic stroke.

9 Appendices

9.1 Literature Review/References

The applicant conducted searches of major databases, PubMed and ISI Web of Knowledge, for literature reporting on safety of epinephrine inhalers from 1950 through 2013. The applicant identified three pertinent case reports[4] describing SAEs. All three described extreme and likely unique cases of misuse or overuse, i.e., injecting the contents of a vial of the aerosol, using an entire vial (200 puffs) over 1-2 days, or using two puffs up to 20 times per day.

We found two additional reports in the literature that address the safety of OTC epinephrine inhalers. One report (Dickinson et. al.[5]) discussed the safe and proper use of OTC inhalers for asthma. The authors identified articles published between 1966 and 1998 describing use of nonprescription inhalers for asthma. They also reviewed postmarketing reports of safety from 1975 until 1997, finding 286 events with 13 deaths (the manufacturer estimated > 115 million Primatene Mist units had been sold over that

3 http://www.aapcc.org/annual-reports/ (accessed January 9, 2014); Bronstein AC, et. al., (2009) *Clin Toxicol*, 47: 911-1084; Bronstein AC, et. al., (2010) *Clin Toxicol*, 48: 979-1178; Bronstein AC, et. al., (2011) *Clin Toxicol*, 49: 910-941; Bronstein AC, et. al., (2012) *Clin Toxicol*, 50: 911-1164; Mowry JB, et. al., (2013) *Clin Toxicol*, 51: 949-1229.
4 Mishra RK, S Radhi, KM Nugent, 2010, A 20-yer-old Woman with Severe Asthma Refractory to Primatene Mist, *CHEST*, 138: 1253-1255; Loria RC, HJ Wedner, 1989, Facial Swelling Secondary to Inhaled Bronchodilator Abuse: Catecholamine-Induced Sialadenosis, *Ann Allergy*, 62: 289-293; Woodard ML, LD Brent, 1998, Acute Renal Failure, Anterior Myocardial Infarction, and Atrial Fibrillation Complicating Epinephrine Abuse, *Pharmacotherapy*, 18: 656-658.
5 Dickinson BD, RD Altman, SD Deitchman, HC Champion for Council on Scientific Affairs, American Medical Association, 2000, Safety of Over-the-counter Inhalers for Asthma, *CHEST*, 118: 522-526.

time period). Three deaths were believed to be the result of concomitant medical conditions, while a relationship to epinephrine could not be determined in the others. Survey data was presented, but survey data often suffers from recall bias. Ultimately, while the authors stated that there were no existing data that the products' availability caused harm for the target population of users with mild, intermittent asthma, they warned that gross misuse or abuse would increase risk for serious AEs, particularly cardiac-related AEs. Their conclusions, adopted as American Medical Association policy in 1999, were 1) to strengthen labeling to better educate all potential users, 2) to encourage FDA to consider the products' appropriateness in the OTC marketplace and, if deemed appropriate, 3) to consider whether product availability is a risk factor for serious asthma-related outcomes.

The final report[6] detailed a small trial of the efficacy of a stepped increase in the number of epinephrine inhaler actuations versus albuterol inhalations in patients with nocturnal asthma symptoms. The authors compared epinephrine's effectiveness, its duration of action and its cardiovascular effects to a same number of doses of albuterol. Eight young and otherwise healthy subjects (20-46 years of age) administered 2, 4 and 8 actuations of epinephrine or albuterol, in a crossover fashion, in 17-minute intervals on two consecutive nights. Mean heart rate changes were significantly different, i.e., 20 bpm higher after albuterol, by the second dose at 17 minutes (6 total actuations). Serum potassium was lower after albuterol as well (3.6 mcmol/L vs. 3.2 mcmol/L).

9.2 Labeling Recommendations

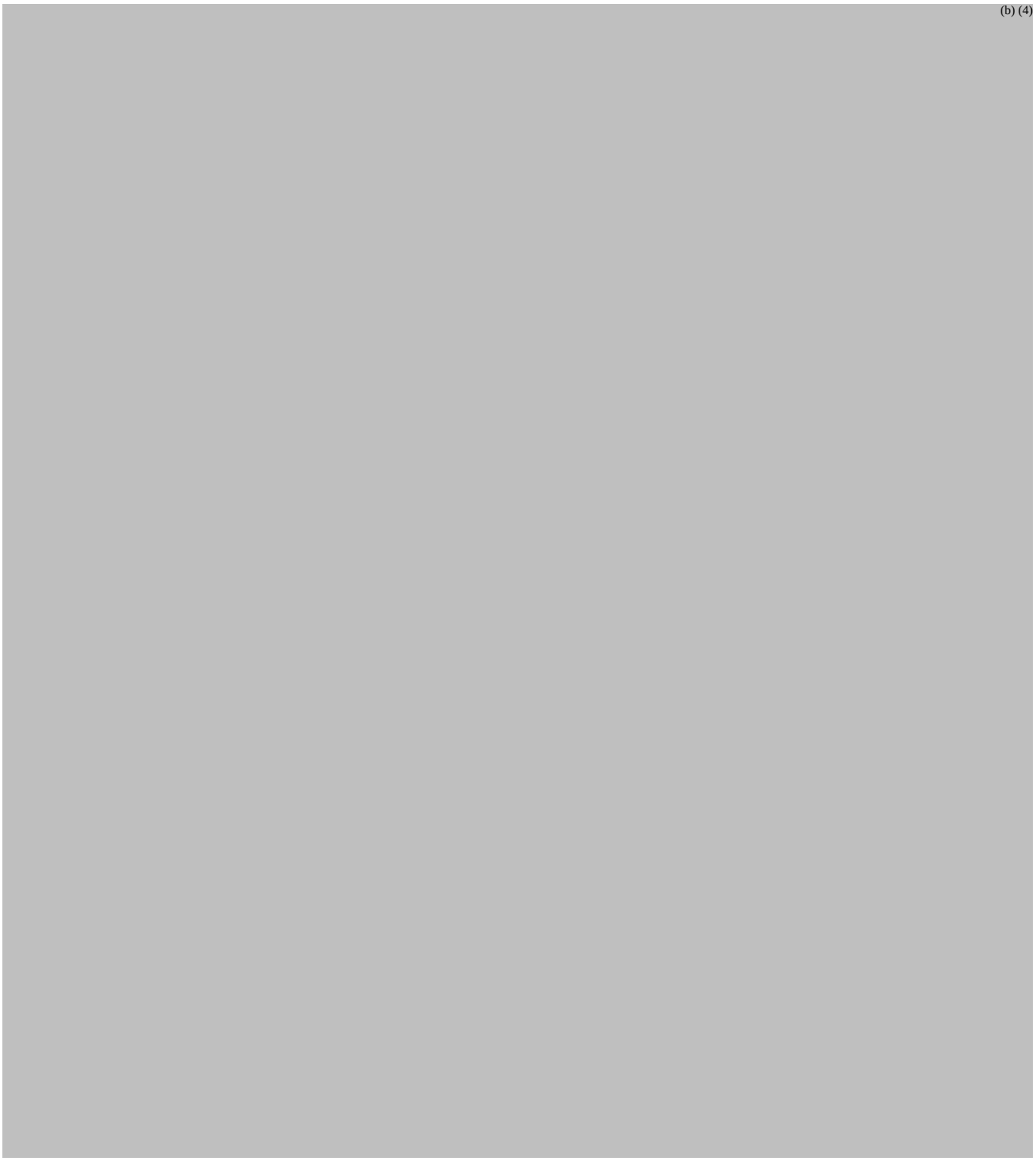
On July 1, 2013, FDA notified the applicant that its proposed tradename, (b) (4) would be denied. (b) (4) Division of Medication Error Prevention and Analysis considered that (b) (4) may lead to confusion and increase risk for errors. Further, the Division considered the (b) (4) The applicant's proposal was withdrawn.

In December 2013, the applicant submitted the proposed tradename (b) (4) for consideration. This reviewer believes that (b) (4) The epinephrine HFA product differs in significant ways from the prior product (see **Table 1** and **Section 2.1 Product Information**). Differentiation of the products is important to ensure safe and proper use of the epinephrine HFA as per its approved indication. Notably, the applicant's assessment of consumer understanding of labeling revealed that some who previously used Primatene Mist assumed that the proposed product could be used in

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

the same manner. Recently, the applicant submitted a proposed top panel to the Principal Display detailing the "Special Directions" necessary to properly use epinephrine HFA ("See Side Panel…"). See **Figure 2** and **Figure 3** for the Principal Display, Special Directions and Drug Facts Label.

(b) (4)



Reviewer's comments: If FDA decides to approve this product, this reviewer has comments for the proposed Drug Facts Label:

- *The proposed "Asthma alert" does not communicate the same magnitude of warning as the Final Monograph (21 CFR 341.76(c)(6)(ii)) label wording. The direction*

to see a doctor if symptoms do not improve or worsen should include a bolded statement [redacted] (b) (4) *Even "mild" asthma may rapidly worsen without prompt medical attention for exacerbations.*

- *Revise the **Warnings** to instruct consumers to see their doctor if they "have* [redacted] (b) (4) *2 asthma attacks in a week."*
- *The portion of the bullet under section "Ask a doctor or pharmacist…" which reads "taking prescription drugs for asthma," should be moved to the section above - "Ask a doctor before use if you."*
- *Remove* [redacted] (b) (4) *"a psychiatric or emotional condition." Consumers taking medication for such conditions are already directed to speak to their pharmacist or doctor, or not to use the product if taking MAOI drugs.*
- *This reviewer is concerned about labeling the drug for use by only adults and children over age 12 years when the product has historically been labeled and used by children as young as four. It is likely that children under age 12 may use the drug if approved.*
  - *The Directions section should state "Children under 12 years of age: Do not use; it is not known if the drug works or is safe in children under 12."*

[redacted] (b) (4)

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

9.3 Advisory Committee Meeting

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. The submitted and distributed briefing material included FDA's summary of the application, detailed review of PK, PD, efficacy and safety information from clinical trials conducted to support the application, postmarketing safety data from the previously marketed Primatene® Mist product, and review of the adequacy and robustness of the MDI itself, including the dose indicator (see http://www.fda.gov/AdvisoryCommittees/Calendar/ucm380886.htm (accessed March 10, 2014) for details and links to the briefing material).

The following were discussed and voted on during the meeting. Additional questions were proposed based on yes/no voting to ascertain the reasons behind the vote:

- Discuss the Efficacy data for epinephrine inhalation aerosol 125 mcg per inhalation. Consider dose selection in the discussion.
- Discuss the safety profile of epinephrine inhalation aerosol 125 mcg per inhalation for the OTC setting.
- Discuss the impact of device performance of epinephrine inhalation aerosol 125 mcg per inhalation on both efficacy and safety.
- **VOTE**: Do the efficacy data provide substantial evidence for the OTC use of epinephrine inhalation aerosol 124 mcg per inhalation in adults and children 12 years of age and older for the proposed indication, " the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath?"
    - The committee voted 14-10 that the efficacy data provide substantial evidence for the proposed indication. Those members voting "yes" acknowledged the well-established efficacy of epinephrine as a bronchodilator and its long history of use. Members who voted "no" raised several concerns (described in more detail below and elsewhere):
        - Lack of "real world" data
        - Only a single efficacy trial was conducted
        - Limited data exist supporting use by adolescents 12-18 years of age
        - The labeled symptoms of asthma, wheezing, tightness of chest and shortness of breath are not specific to intermittent asthma and may not aid consumers in proper selection and use of the product

- **VOTE**: Has the safety of epinephrine inhalation aerosol 125 mcg per inhalation for OTC use in intermittent asthma been adequately demonstrated?
    - The committee voted 17-7 that the safety of the epinephrine HFA has **not** been adequately demonstrated for OTC use. Panelists who voted "yes," that safety was demonstrated, noted the long standing history of the Primatene

product and its postmarketing and cardiac safety. Members who voted "no" raised several concerns (described in more detail below):

- Lack of long term safety data
- Limited data supporting use by adolescents 12-18 years of age
- Issues with the device and dose indicator may impact safety
    - Some panelists questioned product's 160 available doses, wondering whether lesser quantity per product would be more appropriate by limiting potential for overuse.
- Consumers may not be able to adequately assess their asthma severity
- OTC availability of the drug precludes adequate education about asthma and its management by learned intermediaries
    - This led to discussion about holding a future meeting to specifically address the appropriateness of OTC asthma management
- National guidelines clearly recommend against use of epinephrine as a front line asthma treatment

Reviewer's comments: I will address "real world" data and consumer recognition of asthma symptoms below. The adequacy of data from a single efficacy trial (Trial C), including safety data from clinical trials, and data supporting use by adolescents 12-18 is addressed by Dr. Pippins and Ms. Zhao in their reviews. Dr. Pippins' review and those by Ms. Barbara Cohen and Dr. Ramaswamy address the device and dose indicator issues.

At the meeting, the applicant stated that a 160-count product was chosen based on the size of the aluminum canister and the dose indicator available for manufacture and incorporation into the final product. It is reasonable, however, to consider a smaller available quantity of epinephrine per product to potentially improve the safety by limiting overuse. Consumers may also be prompted to see their physicians for more regular asthma care if labeling instructs consumers, particularly high volume users, to do so. If used only once per week, according to national guidelines for intermittent asthma, 64 doses would constitute two months' worth of drug (maximum eight inhalations per week x four weeks x two months). National guidelines are addressed in ***Sections 1.2 Risk Benefit Assessment*** *and* ***2.6 Other Relevant Background Information****.*

- Discuss the proposed Drug Facts label and Consumer Package Insert.
- **VOTE**: Is the risk/benefit profile of epinephrine inhalation aerosol 125 mcg per inhalation supportive of OTC use for the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath in adults and children 12 years of age and older?
    - The committee voted 18-6 that the risk/benefit profile **does not** support OTC availability and use of epinephrine HFA. "No" votes echoed the concerns

raised in discussion of the previous voting question regarding safety. Other concerns included:

- The name "Primatene" or "Primatene Mist" should not be under consideration as a tradename if the product is approved. The epinephrine HFA is a different product than Primatene Mist, and any confusion between use of the two products should be limited.
- Also dependent on future approval, the color and design of the device should distinguish it from all other inhalers for asthma management, as patients frequently identify their inhalers by the color and shape, not the name of the product.

While data from the conducted clinical trials appear to support efficacy when the product is used as directed, the committee expressed concern that there were no data to evaluate "real world" use of the product. It considered experience in clinical practice, anecdotal reports from the public and postmarketing reports of use of the previously marketed Primatene Mist product. With that information, the committee's concern is for potential off label use of the product for all types of respiratory symptoms and use not necessarily according to labeling for the intended indication.

Reviewer's comments: This reviewer does not agree that there were none or inadequate "real world" use data, or that consumer behavior data in the form of an Actual Use Study would be necessary to address some of the committee members' concerns. Early in product development, in 2007, FDA asked for a "real world" study to be conducted to determine whether consumers using the product seek appropriate medical care when needed, if they are likely to overuse the product or if they may undertreat more severe asthma symptoms. Over time, thinking evolved, and we believed that adequate data could be collected from long term safety evaluation and behavioral use (human factors) evaluation. Regarding Actual Use Studies, these provide information on whether consumers are likely to use an OTC product safely and properly in the "real world." However, there are several reasons why data may be adequate from other sources, e.g., safety and efficacy trials, other consumer behavior studies, and postmarketing experience:

- *Safety and efficacy trials (C, C2 and D) were conducted with adults and children as young as four years old for up to 24 weeks with regularly scheduled visits interspersed between consistent, daily, at-home use of epinephrine HFA, active control (Primatene Mist) or placebo.*
  - *At-home use, including priming, actuation and cleaning procedures were assessed, although use technique was ensured prior to enrollment and MDI use training was conducted at each visit in Trials C and D (not Trial C2).*
    - *Primary objectives of these trials included evaluation of device performance and functionality and reliability of the dose indicator.*
- *Three iterative Label Comprehension Studies and one demonstration (human factors) study were conducted. There were also pilot demonstration portions of the Label Comprehension evaluation. The studies evaluated understanding of*

use of the dose indicator and directions for actuation, cleaning, priming and re-priming. See Barbara Cohen's review.

- *Generally, Actual Use Studies are conducted for products undergoing a switch from prescription-only to OTC marketing status to help determine whether there are concerns of safety or effectiveness after consumers are free to purchase and use a product based on its Drug Facts Label alone and without the involvement of a learned intermediary.*
  - *Primatene Mist was available OTC for several decades.*
  - *Data exist, from those several decades, to support use of an epinephrine inhalation aerosol for OTC management of asthma.*
  - *Note that due to differences between Primatene Mist and epinephrine HFA, extrapolation of postmarketing safety from Primatene Mist to the proposed product warrants caution.*
- *In the form of an Actual Use or Self-selection assessment, it may be difficult to adequately ascertain whether the proper population, asthmatics with only mild symptoms of intermittent disease, selects to purchase and use the product for the proposed indication.*
  - *Direct advisement on symptoms or frequent follow up with investigators or physicians to monitor whether subjects are properly choosing to use the product for mild exacerbations are not commonly performed in Actual Use Studies because they limit the "real world" experience, i.e., limited to no involvement of a learned intermediary.*
  - *Mild exacerbations may also be so infrequent that assessment of proper use of the product may be limited or inadequate to be considered generalizable to OTC consumers.*

Ultimately, we will consider all of the submitted data, prior experience with an epinephrine MDI in the OTC setting, national guidelines on diagnosis and management of asthma, and the Advisory Committees' deliberations. If we decide to approve epinephrine HFA, adequate labeling will be negotiated by the review team and the applicant with consideration of all sources of information.

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/s/

RYAN M RAFFAELLI
04/15/2014

LUCIE L YANG
04/15/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205-920
Priority or Standard	Standard
Submit Date(s)	July 20, 2013
Received Date(s)	July 22, 2013
PDUFA Goal Date	May 22, 2014
Division / Office	DPARP/OND
Reviewer Name(s)	Jennifer Rodriguez Pippins, MD, MPH
Review Completion Date	April 11, 2014
Established Name	Epinephrine Inhalation Aerosol
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Non-selective alpha- and beta-receptor agonist
Applicant	Armstrong Pharmaceuticals
Formulation(s)	Orally inhaled
Dosing Regimen	1 to 2 inhalations
Indication(s)	Asthma
Intended Population(s)	Adults and children ≥ 12 years

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

At the time of this review, the recommended regulatory action from a clinical perspective for epinephrine inhalation aerosol 125 mcg/inhalation for the temporary relief of mild symptoms of intermittent asthma in adults and adolescents 12 years of age and older is Complete Response. While the clinical program provides evidence of the proposed product's efficacy as a bronchodilator, and while the clinical trial safety data is adequate to support approval, the review of the Application has identified questions about device robustness and reliability, which are sufficiently concerning from a safety perspective to warrant the recommendation of a Complete Response. The review of the chemistry, manufacturing, and controls (CMC) data is ongoing at this time; therefore, the clinical review team's recommendation of a Complete Response is preliminary and subject to change upon completion of the CMC review.

1.2 Risk Benefit Assessment

The proposed indication for epinephrine inhalation aerosol 125 mcg/inhalation (hereafter referred to as epinephrine-HFA) is the temporary relief of mild symptoms of intermittent asthma in adults and adolescents 12 years of age and older. The product is proposed for over-the-counter (OTC) use. If approved, it would be the only metered dose inhaler (MDI) available over-the-counter.

Evidence of efficacy comes primarily from Trial C, a randomized, double-blind or evaluator-blind, placebo-controlled and active-controlled, parallel group trial with a 12-week treatment duration conducted in a population of adults and adolescents. The primary efficacy endpoint in Trial C was mean area under the curve (AUC) of ΔFEV1 (% change from same-day baseline FEV1) versus time ($AUC_{\Delta\%}$), at study Visit 5 (Week 12). Results for the primary endpoint demonstrate statistical significance for the comparison between epinephrine-HFA and placebo, and are robust to the various methods of missing data handling and population definitions. Results for Primatene® Mist are also statistically significant, with a magnitude of effect that is similar to that demonstrated for epinephrine-HFA. The results for additional spirometric endpoints, including serial FEV1 (L) from baseline to 360 minutes post-dose, at the start and end of treatment in Trial C (i.e., Day 1 and Week 12), were supportive of the primary endpoint. Spirometry is an appropriate choice of endpoint for a purported bronchodilator, and the magnitude of effect demonstrated for epinephrine-HFA is likely to be clinically meaningful. Taken together, these data provide evidence of epinephrine-HFA's efficacy as a bronchodilator.

The premarket safety database for the proposed product consists of a 3-month phase 3 trial conducted in adults and adolescents 12 years of age and older (Trial C), combined with a 12-week extension (Trial C2). Patients enrolled in the extension were permitted to have up to a 135-day interruption in trial participation. Additional safety data is provided by a 4-week trial in pediatric patients ages 4 to 11 years. The safety database and extent of exposure were adequate to permit review. There were no deaths in the clinical development program, and only three serious adverse events (SAE). There was a low number of events leading to discontinuation, and the percentage of patients with any adverse event (AE) leading to discontinuation is balanced between the epinephrine-HFA and placebo treatment arms.

The clinical development program prospectively identified adverse events of special interest (AESI), based on the known clinical and pharmacological effects of epinephrine. Given the increase in systemic exposure documented for epinephrine-HFA compared to Primatene® Mist, particular attention was paid to systemic effects including cardiovascular effects. Adverse events designated as AESIs were tremor, chest discomfort, chest pain, tachycardia, heart rate increase, and QTc prolongation. Tremor was the most commonly reported AE for patients treated with epinephrine HFA in Trials C and C2 combined, and a notable imbalance between the proposed product and placebo is observed (10% vs. 2%, respectively); this result is expected. Chest discomfort and chest pain were more common for the epinephrine-HFA treatment arm compared to placebo, but the low number and benign nature of the observed events are reassuring. The observed mean changes in vital signs in Trial C and C2 were either balanced across treatment groups or not likely to be of clinical relevance, as were observed changes in QTc on electrocardiograms. Premature ventricular contractions (PVCs) were more common for epinephrine-HFA compared to placebo in Trial C, although the overall number of events was low. No arrhythmias were reported for either Trial C or C2. A consult review obtained from the Division of Cardiorenal Product concludes that while the total exposure in the clinical development program would allow only for the identification of catastrophic cardiovascular events, reassurance is provided by the totality of the data, which includes the absence of cardiac events in the clinical development program, projections of minimal consequences of the immediate effects of epinephrine-HFA upon vital signs, and the benign postmarketing experience with Primatene® Mist.

The approval of a new drug product takes into account not only the evidence to support efficacy and safety, but also chemistry, manufacturing, and controls data. The device performance data for epinephrine-HFA call into question the device robustness and reliability. Of particular concern is the high percentage of devices reported as malfunctioning (7%) observed in the phase 3 clinical trials; typically, device malfunctions are rare and not seen in premarket registration trials. The types of malfunction included clogging and failure to properly dispense, which occurred in spite of the priming, dosing, and cleaning procedures detailed in the trial protocol. Also concerning are the reports

of dose indicator errors in the Phase 3 trials and, in particular, dose indicator undercounting. Dose indicator undercounting leads to an overestimation of the number of remaining actuations. This is particularly problematic for a product proposed for use as a quick-relief medication, as it presents a safety concern. While the focus of this clinical review is on the premarket efficacy and safety data provided by the epinephrine-HFA development program, the CMC data is an important element of FDA's review, and it is the clinical review's team's assessment that questions about device robustness and reliability are sufficiently concerning from a safety perspective to warrant the recommendation of a Complete Response. It should be noted that the review of the CMC data is ongoing at this time; therefore, the clinical review team's recommendation of a Complete Response is preliminary and subject to change upon completion of the CMC review. In addition, it should be noted that the appropriateness of the OTC setting for a product intended for the treatment of asthma was questioned at the February 25, 2014, Advisory Committee Meeting held for this application; this remains a topic of ongoing internal discussion within the Agency at this time.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

As the clinical review recommendation is against approval, recommendations for postmarket risk evaluation and mitigation strategies are not discussed.

1.4 Recommendations for Postmarket Requirements and Commitments

As the clinical review recommendation is against approval, recommendations for postmarket requirements and commitments are not discussed.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed product is a metered dose inhaler (MDI) composed of an anodized aluminum canister with metering valve, a top mounted dose indicator, and an L-shaped actuator with dust cap. The formulation contains a suspension of epinephrine in HFA-134a propellant, ethanol, thymol, and polysorbate 80. Thymol (b) (4) and polysorbate 80 (b) (4) are two excipients not frequently present in inhalation products, and were not present in Primatene® Mist.

Each epinephrine-HFA MDI contains 160 metered dose inhalations, with 125 mcg of epinephrine per inhalation. The instructions on the package insert direct the user to shake and prime the MDI prior to use, and to disassemble and clean the product daily. In the pivotal efficacy trial (Trial C) the epinephrine-HFA device was primed 4 times prior to first dose and re-primed 2 times after two weeks of non-use; no priming was required for the Primatene® Mist comparator. The dosing procedure for Trial C included instructions for patients to shake the epinephrine-HFA device vigorously for several seconds immediately before each inhalation; no shaking was required for Primatene® Mist. The cleaning procedure for Trial C included instructions for patients to disassemble and clean the epinephrine-HFA device daily, preferably after the last evening dosing to allow for air-drying time; patients in the Primatene® Mist arm were instructed to clean the mouthpiece after each use.

FDA's review of the application has identified issues regarding device robustness and reliability. Of particular concern is the high percentage of devices reported as malfunctioning (7%) observed in the phase 3 clinical trials; typically, device malfunctions are rare and not seen in premarket registration trials. The types of malfunction included clogging and failure to properly dispense, which occurred in spite of the priming, dosing, and cleaning procedures detailed in the trial protocol. Also concerning are the reports of dose indicator errors in the Phase 3 trials and, in particular, dose indicator undercounting. Dose indicator undercounting leads to an overestimation of the number of remaining actuations. This is particularly problematic for a product proposed for use as a quick-relief medication, as it presents a safety concern. The assessment of the CMC data for this application remains ongoing at the time of this review.

2.2 Tables of Currently Available Treatments for Proposed Indications

Asthma is a chronic disease characterized by inflammation of the airways and episodic airflow obstruction. Drug therapies for asthma are classified into two broad categories corresponding to these two aspects of the disease: (1) Controller medications that address the underlying inflammation, and (2) reliever medications that address the episodic airflow obstruction. Examples of medications belonging to each of these two therapeutic categories are provided in Table 1. This table (with some modification) is based on the recommendations outlined in the 2007 NHLBI National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR3) and reflects the current standard of care for asthma.

Table 1. Drug therapies for asthma

Class	Example
Controller Medications	
Corticosteroids Inhaled corticosteroids (ICS)	 Beclomethasone dipropionate Budesonide Ciclesonide Flunisolide Fluticasone propionate Mometasone furoate Triamcinolone acetonide
Oral systemic corticosteroids*	Methylprednisolone Prednisolone Prednisone
Long-acting beta$_2$-agonists (LABA)[#]	Formoterol Salmeterol
ICS/long-acting beta$_2$-agonists (ICS/LABA)	Fluticasone propionate/salmeterol Budesonide/formoterol Mometasone/formoterol
Leukotriene modifiers Leukotriene receptor antagonists (LTRA) 5-lipoxygenase inhibitor	 Montelukast Zafirlukast Zileuton
Mast cell stabilizers	Cromolyn sodium Nedocromil
Immunomodulators	Omalizumab
Methylxanthines	Theophylline
Quick-Relief Medications	
Short-acting beta$_2$-agonists	Albuterol Levalbuterol
Non-selective adrenergic agents	Epinephrine Racepinephrine

*oral systemic corticosteroids are used as a long-term controller in severe persistent asthma; they are also used during exacerbations
[#]Recommended only in combination with inhaled corticosteroids

2.3 Availability of Proposed Active Ingredient in the United States

Since the phase-out of Primatene® Mist on December 31, 2011, there has been no epinephrine inhalation product approved under an NDA or ANDA in the United States; however, the monograph for OTC bronchodilators (i.e., epinephrine and racepinephrine) administered by hand-held rubber bulb nebulizer has remained in effect (21CFR341.16 and 21CFR341.76).

2.4 Important Safety Issues With Consideration to Related Drugs

Epinephrine is a non-selective alpha and beta agonist. Concerns were raised about the possible link between the use of inhaled epinephrine and asthma-related death in the 1940s.[1] The 1950s and 1960s brought the introduction of new inhalation products for asthma to the market worldwide, including non-selective (β1 and β2) short-acting beta agonists (SABA) such as isoproterenol and fenoterol, which were both implicated in asthma-related deaths in certain countries outside of the United States.[2,3,4,5,6] The use of these relatively non-selective beta agonists was eventually replaced by more selective (β2) short-acting beta agonists, e.g., albuterol and levalbuterol. Albuterol, which may be delivered by metered dose inhaler (MDI) or electronic nebulizer, is used broadly today as the quick-relief medication of choice for asthma. Concerns have been raised in the medical literature about the association of albuterol and other inhaled beta agonists and asthma-related death;[7,8] but the topic remains controversial and has been the extensively discussed at prior FDA Advisory Committee meetings and in the literature.[9,10,11,12]

The 2007 NAEPP EPR3 recommends short-acting $beta_2$-agonists as the drug class of choice for rescue treatment, describing SABAs as "the most effective medication for relieving acute bronchospasm."[13] The 2007 NAEPP EPR3 also notes that currently

[1]Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. *J Allergy.* 1948;19:129-140.
[2]Van Metre TE. Adverse effects of inhalation of excessive amounts of nebulized isoproterenol in status asthmaticus. *J Allergy.* 1969;43:101-113.
[3]Crane J, Pearce N, Flatt A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-83:case-control study. *Lancet.* 1989;1:917-922.
[4]Grainger J, Woodman K, Pearce N, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-1987: a further case-control study. Thorax. 1991;46:105-111.
[5]Westendrop RG, Blauw GJ. End of New Zealand asthma epidemic. *Lancet.* 1995;345:985.
[6]Spitzer WD, Suissa S, Ernst P. The use of beta-agonist and the risk of death and near death from asthma. *N Eng L Med*. 1992;326:501-506.
[7]Suissa S, Ernst P, Bolvin, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta agonists. *Am J Resp Crit Care Med*. 1994;604-610.
[8]Mullen M, Mullen B, Carey M. The association between beta-agonist use and death from asthma. *JAMA*. 1993;270:1842-1845.
[9]Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; and Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008.
[10]Martinez FD. Safety of long-acting beta-agonists – an urgent need to clear the air. *New Eng J Med* 2005; 353:2637-2639.
[11]Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists – the influence of values. *New Eng J Med* 2009; 360:1952-1955.
[12]Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. *New Eng J Med* 2009; 360:1671-1672.
[13]2007 NHLBI National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3, pg. 236.

available SABAs "have few negative cardiovascular effects." [14] This stands in contrast to the NAEPP assessment of epinephrine and other less selective adrenergic agents:

> *The less beta$_2$-selective agents (isoproterenol, metaproterenol, isoertharine, and epinephrine) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.*[15]

While FDA acknowledges the NAEPP's position, it should be noted that an epinephrine MDI was approved in 1956. Epinephrine MDIs have been marketed over-the-counter for over 50 years prior to discontinuation in 2011, in compliance with the phase-out of ozone-depleting CFC under the Montreal Protocol.[16] The discontinuation of epinephrine-CFC-MDI was not due to any patient safety concerns.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Epinephrine-HFA is related to a formerly marketed epinephrine MDI product containing CFC as a propellant (Primatene® Mist). Primatene® Mist was marketed OTC. Primatene® Mist is no longer available in the United States since December 31, 2011, due to the phase-out of products containing CFCs outlined by the Montreal Protocol.

Epinephrine was first approved as an OTC MDI under an NDA in 1956, and Primatene® Mist (NDA 16-126, Wyeth) was approved in 1967. A generic version, epinephrine CFC-MDI (ANDA 87-997, Armstrong [a subsidiary wholly owned by Amphastar]) was approved in 1984. Armstrong subsequently purchased the Primatene® Mist trademark and Wyeth withdrew NDA 16-126 and discontinued distribution of the product. Armstrong's product was available in a 220 mcg/inhalation formulation, and indicated for the "temporary relief of occasional symptoms of mild asthma: wheezing, tightness of chest, shortness of breath" in adults and children 4 years of age and older. The dosing recommendation across the entire age spectrum was:

> "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."

Several interactions between the Agency and the Sponsor have previously taken place:

- **March 27, 2007 pre-IND meeting**

[14] Ibid.
[15] 2007 NHLBI National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3, pg. 247.
[16] FDA News Release, September 22, 2011, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm272872.htm, accessed December 20, 2013.

- The Agency provided general recommendations for the proposed epinephrine HFA development program, including requirements for clinical efficacy and safety, consumer behavior studies, and data to support the reliability and robustness of the device and dose counter.

- **November 25, 2008 Communication, feedback provided to Sponsor**
  - The Agency provided feedback to questions submitted by the Sponsor regarding the appropriate spirometric parameters, patient population, study duration, and dosing schedule to be assessed in the initial clinical trial.

- **February 20, 2009 Teleconference**
  - The Agency encouraged the Sponsor to develop outreach programs to educate consumers of the impending phase-out of the epinephrine CFC-MDI product.

- **October 26, 2009 IND submitted to the Agency and allowed to proceed**
  - Written feedback provided by the Agency regarding the proposed development program, including the need for detailed monitoring of cardiovascular vital signs, pharmacokinetic sampling, long-term safety data, consumer studies, and data to support the chemistry, manufacturing, and controls of the product.

- **October 29, 2010 EOP2 Meeting; feedback provided to the Sponsor included the following:**

  Dose Ranging
  - Dose-ranging did not appear to be adequate
  - The systemic exposure associated with the proposed 2 x 125 mcg/inh dose was noted to be higher than that of the reference product
  - It was recommended that the Sponsor explore doses lower than 125 mcg/inh

  Proposed Pediatric Trial (API-E004-CI-D)
  - The proposed 2 pediatric trial was too small (n=48) and too short in duration (2 weeks) to provide adequate safety data
    - The Sponsor replied that they intended to conduct a 4-week pediatric trial

  Phase 3 Trial Design
  - The Agency communicated to the Sponsor that the Phase 3 placebo-controlled trials should include the reference product.

  Assessment of Device Performance

  - The Agency reminded the Sponsor that the clinical program should include a robust evaluation of human factors and demonstration of device ruggedness and reliability.

- **May 10, 2011 Communication; the Agency provided the following feedback:**
  - Based on the results of additional trials (E004-A2 and E004-B3) conducted by the Sponsor, along with the previously conducted phase 2 trials (E004-A and E004-B), the Agency did not agree with the proposed 180 mcg dose for the P3 program
  - While 90 mcg X 2 inh (180 mcg total dose) appeared to offer greater benefit (in terms of FEV1) than Primatene® Mist 220 mcg x 2 inh, 90 mcg x 1 inh offered an inferior benefit compared to Primatene® Mist 220 mcg x 1 inh. The Agency explained that this was undesirable, given that the Primatene® Mist label advises that consumers start with 1 inhalation, with a second inhalation to be used only if there is insufficient relief after at least 1 minute
  - The Agency recommended carrying forward the E004 125 mcg dose into the Phase 3 program, noting that the systemic exposure from E004 125 mcg is higher than that with Primatene® Mist 220 mcg, a difference that will have to be supported by Phase 3 data and addressed in the NDA
- **June 22, 2011 Communication**
  - The Agency asked the Sponsor to provide information concerning communication efforts being made regarding their product's anticipated phase-out, as well as an update on when the remaining supply of epinephrine CFC inhalers would be exhausted
- **September 23, 2011, preNDA meeting; feedback provided to the Sponsor included the following:**
  - Reiteration of the need for a minimum of 6 months of safety data
  - The need for a large (n~300) label comprehension/behavioral use trial
  - Concern regarding the product's potential need for once-daily cleaning. The Agency requested that the Sponsor provide performance data under different in-use conditions to assess the impact of not cleaning the mouthpiece as directed.
  - Reminder to assess potential malfunctioning of the device with real-life usage
  - Recommendation that the Sponsor request a second pre-NDA meeting upon the completion of phase 3
  - The application is not likely to qualify for fast track designation
- **January 26, 2012, Communication**

  - The Agency communicated a request for safety data from at least 300 patients exposed for 6 months, which could be generated from already ongoing trials or from a new separate long term safety trial
  - To inform the evaluation of safety, the Agency requested PD data (i.e. blood pressure, heart rate)
  - The Agency noted that it was difficult to comment on the adequacy of the proposed pediatric problem at the time of communication, and recommended that they not proceed with additional pediatric studies until efficacy and safety data in adults and adolescents was available

- **April 23, 2012, Communication; feedback provided to the Sponsor on proposed label comprehension study**
- **January 31, 2013, preNDA meeting; feedback provided to the Sponsor included the following:**
  - An evaluation of device performance during real-life use, evidence of device ruggedness, and a discussion of the potential for device clogging needed to be included in the NDA submission
  - Justification for the device cleaning instructions should be submitted
  - Frequency blood pressure and heart rate measurements around Cmax were requested, as well as at Tmax
  - Detailed descriptions of chest pain AEs, AEs leasing to discontinuation, and serious AEs should be submitted
  - An analysis of the literature, AERS data, and the Applicant's post-marketing database should be submitted
  - Mean serial FEV1 over time should be submitted
  - The adequacy of the pediatric program to support approval in children 4 to 11 years of age would be a review issue; Amphastar stated that they may submit the NDA for adults 18 years of age and older. FDA noted that this proposed restriction to adults for the initial submission would be a review issue, given that the original Primatene® Mist product was labeled down to 4 years of age, and the concern that the new product would be used in this age range even if only approved for adults. FDA advised the Applicant to submit all pediatric data with the NDA application, even if the age range proposed for approval is limited to adults.
  - The decision regarding an advisory committee meeting would be made after NDA submission, and would depend on both the nature of the data submitted as well as on an assessment of public health issues pertinent to the application.

- **April 8, 2013, NDA 205-496 was submitted for epinephrine-HFA, but the application was noted to have a number of deficiencies that precluded substantive review, and so was not accepted by FDA (i.e., refused filing)**
- **July 20, 2013, NDA 205-920 was submitted for epinephrine-HFA and accepted for filing**

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was appropriately indexed and complete to permit review.

An Office of Scientific Investigations (OSI) consult was requested. A center effect analysis was conducted by the primary statistical reviewer for the main efficacy trial (Trial C). This analysis took into account the magnitude of the treatment effect for the primary endpoint, the number of patients, and the percent dropout per site. While no one site appeared likely to drive efficacy results, based on the analysis the clinical recommendation was for audit of site 18 and site 20, as they were characterized by a high enrollment, large percentage of dropouts, and a large effect size. The final classification for these inspections was NAI (no deviation from regulations), and OSI has recommended that the data from Trial C be considered reliable. In addition to the two site inspections, a Sponsor Inspection was also conducted. The final classification for the Sponsor inspection is pending at this time; the preliminary assessment is also NAI.

3.2 Compliance with Good Clinical Practices

For each of the trials discussed in this review, the clinical study report states that the trial was undertaken in accordance with the current ICH Good Clinical Practice (GCP) guidelines and that informed consent was obtained for all subjects.

3.3 Financial Disclosures

The application includes a statement certifying that clinical investigators: 1) did not participate in any financial arrangement with the sponsor whereby the value of compensation to the investigator for conducting the study could be affected by the study's outcome, 2) had no proprietary interest in the product or significant equity

interest in the sponsor, and 3) was not the recipient of significant payments of other sorts.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review is pending at this time. A description of issues regarding device robustness and reliability, and their implications for safety, is provided in Section 2.1.

4.2 Clinical Microbiology

The recommendation from the product quality team is Approval.

4.3 Preclinical Pharmacology/Toxicology

The final recommendation from the pharmacology/toxicology review team is pending at this time; however, no approvability issues have been identified thus far.

4.4 Clinical Pharmacology

The Office of Clinical Pharmacology finds the application to be acceptable from their perspective.

4.4.1 Mechanism of Action

Epinephrine is a non-selective alpha- and beta-receptor agonist.

4.4.2 Pharmacodynamics

The epinephrine-HFA development program included three pharmacokinetic (PK) trials in healthy volunteers (Trials B, B2, and B3) and two dose-ranging trials in adult asthma patients (Trials A and A2), which are summarized in Table 1. The discussion of pharmacodynamics included in this clinical review focuses dose selection and

cardiovascular effects; a more detailed review of the proposed product's pharmacokinetics may be found in FDA's Clinical Pharmacology Review.

Table 1. Pharmacokinetic and Dose-ranging Trials

Trial *Year completed*	Design	N	Treatments	Duration	Primary Endpoint	Number of Sites *% of patients from US*
Dose-ranging trials in adult asthma patients						
API-E004-CL-A (Trial A) *2010*	R, DB or EB, PC, AC, CO	26 26 26 26 26	Epinephrine-HFA 2x125 mcg/inh Epinephrine-HFA 2x160 mcg/inh Epinephrine-HFA 2x220 mcg/inh Epinephrine-HFA Placebo-HFA Primatene® Mist 2x220 mcg/inh	Single dose	AUC of Δ%FEV1	4 *100%*
API-E004-CL-A2 (Trial A2) *2011*	R, DB or EB, PC, AC, CO	30 30 30 30 30 30 30	Epinephrine-HFA 1x90 mcg/inh Epinephrine-HFA 1x125 mcg/inh Epinephrine-HFA 2x90 mcg/inh Epinephrine-HFA 2x100 mcg/inh Epinephrine-HFA 2x125 mcg/inh Epinephrine-HFA Placebo-HFA Primatene® Mist 1x220 mcg/inh Primatene® Mist 2x220 mcg/inh	Single dose	AUC of Δ%FEV1	5 *100%*
Pharmacokinetic trials in healthy volunteers						
API-E004-CL-B (Trial B) *2010*	R, EB, CO	24 22 22	Epinephrine-HFA-D3 10x125 mcg/inh Epinephrine-HFA-D3 10x160 mcg/inh Primatene® Mist 10x220 mcg/inh	Single dose	AUC, C_{max}	1 *100%*
API-E004-CL-B2 (Trial B2) *2010*	R, EB, CO	23 23	Epinephrine-HFA-D3 10x125 mcg/inh Primatene® Mist 10x220 mcg/inh	Single dose	AUC, C_{max}	1 *100%*
API-E004-CL-B3 (Trial B3) *2011*	R, EB, CO	23 23 22	Epinephrine-HFA-D3 12x90 mcg/inh Epinephrine-HFA-D3 12x100 mcg/inh Primatene® Mist 12x220 mcg/inh	Single dose	AUC, C_{max}	1 *100%*

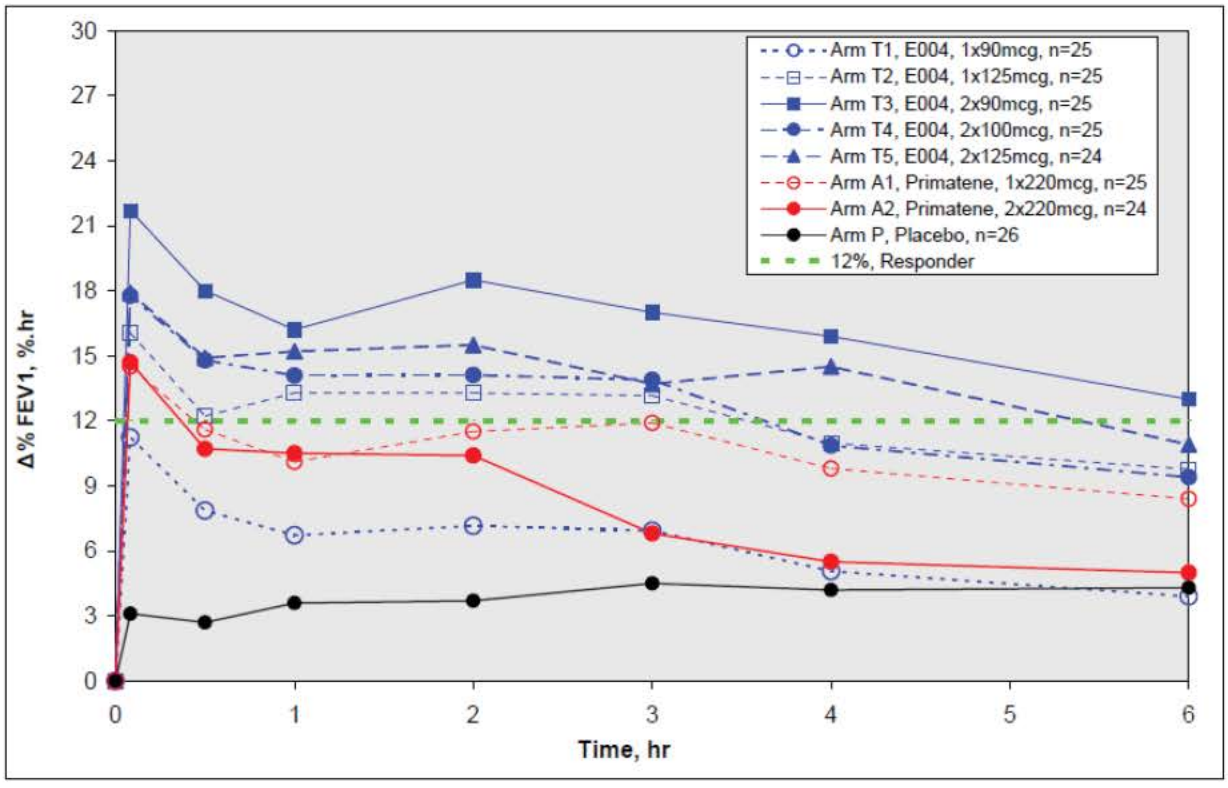
Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.2 (Tabular Listing of All Clinical Studies), pg. 5 (Table 5.2-1); pg. 6 (Table 5.2-2);
Note: N=number in ITT population
Key: AC=active-controlled, CO=crossover, DB=double-blind, EB=evaluator blind, PC=placebo-controlled, R=randomized

Dose Selection

Trials A and A2 were randomized, double-blind or evaluator blind, placebo-controlled and active-controlled (Primatene® Mist), crossover dose-ranging trials in adult patients with asthma. Doses of epinephrine-HFA ranging from 1x90 mcg/inh to 2x220 mcg/inh were evaluated across these two trials.

At an End-of-Phase 2 (EOP2) meeting held on October 29, 2010, the Applicant was informed that trials conducted thus far (Trial A and Trial B) were inadequate to support dose selection. Results from Trial A did not allow for discrimination between the epinephrine-HFA doses evaluated; in addition, Trial B demonstrated a higher systemic exposure (C_{max} and AUC) with the proposed epinephrine 2x125 mcg/inh dose compared to the reference product. The evaluation of lower doses was recommended. In response to this, the Applicant conducted a second dose-ranging trial (A2). An additional PK trial was also conducted (B3).[17] Results for Δ%FEV1 from Trial A2 are provided in Figure 1.

Figure 1. Results for the Primary Endpoint, Δ%FEV1, Trial A2



Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-A2, Study Report), pg. 101 (Figure 7-2)
Key: E004=epinephrine-HFA

[17]The second PK trial (B2) was underway at the time of the EOP2 meeting.

The treatment associated with the greatest degree of bronchodilation is epinephrine-HFA 2x90 mcg/inh, which demonstrates separation from both placebo and the reference Primatene® Mist 2x220 mcg/inh. In contrast, epinephrine-HFA 1x90 mcg/inh dose offers an inferior benefit compared to the Primatene® Mist 1x220 mcg/inh arm. This latter comparison is important, in that the Primatene® Mist product label advised consumers to start with one inhalation, and then to administer a second inhalation only if there was insufficient relief. To that extent, an adequate response is required for both the single and dual inhalations.

Results for C_{max} and AUC from the two of the three PK trials conducted in healthy volunteers are provided in Table 2 .

Table 2. AUC and Cmax for epinephrine-HFA and Primatene® Mist, Trials B and B2

	Epinephrine-HFA		Primatene® Mist	
Trial	**B**	**B2**	**B**	**B2**
N	24	23	22	23
Dose (mcg)	10x125 mcg/inh	10x125 mcg/inh	10 x 220 mcg/inh	10x220 mcg/inh
$AUC_{0\text{-}6hr}$ (pg/mL*min)	7938	8500	7218	6190
C_{max} (pg/mL)	340	860	139	190

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.3.1 (API-E004-CL-B, Study Report), pg. 81 (Table 7-4); Section 5.3.3.1 (API-E004-CL-B2, Study Report), pg. 80 (Table 7-5)

A higher systemic exposure is observed for the proposed epinephrine-HFA product compared to the Primatene® Mist reference product. Nevertheless, given the lesser benefit observed for the 1x90 mcg/inh compared to the 1x220 mcg/inh dose of Primatene® Mist , FDA recommended that the 125 mcg dose be evaluated in the Phase 3 program (Written Communication dated May 10, 2011). At that point in the development program, the Sponsor intended the epinephrine-HFA product to be a full replacement for the CFC product which was still on the market at that time, retaining the same labeled dosing instructions as Primatene® Mist 220 mcg. Therefore, FDA recommended the epinephrine-HFA dose that appeared to most closely approximate the pharmacodynamics of Primatene® Mist 220 mcg. In that same communication FDA noted that the exposure for the epinephrine-HFA 125 mcg dose was higher than that for Primatene® Mist 220 mcg, and that the difference in systemic exposure would need to be supported by the Phase 3 safety data.

Cardiovascular Effects

The effect of high-dose epinephrine-HFA on cardiovascular parameters (systolic blood pressure, diastolic blood pressure, and heart rate) in healthy volunteers was evaluated in Trials B, B2, and B3. Of the three trials, Trial B is the most informative as it was the only study to include a measurement of vital signs before the 30 minute post-dose time

point (i.e., at 10 minutes). Mean change in systolic blood pressure, diastolic blood pressure, and heart rate in Trial B are provided in Table 3.

Table 3. Mean Change in Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate, Trial B

	Epinephrine-HFA 10 x 125 mcg/inh N=24		Epinephrine-HFA 10 x 160 mcg/inh N=23		Primatene® Mist 10 x 220 mcg/inh N=22	
	Mean	Mean Δ (Upper 95% CI)	Mean	Mean Δ (Upper 95% CI)	Mean	Mean Δ (Upper 95% CI)
Systolic Blood Pressure (mmHg)						
0 min	110	--	112	--	111	--
10 min	123	13.2 (16.6)	122	9.7 (14.9)	121	10.8 (13.8)
30 min	116	6.3 (9.5)	117	4.7 (9.1)	116	5.0 (8.3)
60 min	113	2.5 (5.3)	113	0.9 (5.8)	115	4.6 (7.6)
120 min	112	1.5 (4.2)	114	1.5 (5.3)	114	3.5 (6.5)
180 min	114	4.1 (6.7)	113	0.5 (4.8)	115	4.0 (7.6)
360 min	113	3.0 (5.6)	113	1.3 (6.2)	113	2.0 (5.4)
Diastolic Blood Pressure (mmHg)						
0 min	62	--	61	--	61	--
10 min	63	0.7 (2.6)	64	2.4 (4.8)	65	3.6 (6.4)
30 min	64	1.6 (3.8)	64	3.1 (6.0)	65	3.3 (6.3)
60 min	63	1.3 (3.3)	64	2.6 (5.3)	63	1.9 (5.1)
120 min	61	-1.4 (0.4)	63	1.8 (4.1)	62	1.0 (4.3)
180 min	62	0.3 (2.7)	60	-1.6 (0.8)	59	-2.5 (0.6)
360 min	62	0.0 (2.1)	62	0.5 (2.9)	62	0.5 (3.0)
Heart Rate (bpm)						
0 min	60	--	62	--	58	--
10 min	67	6.6 (9.5)	69	6.8 (9.1)	62	4.6 (6.9)
30 min	63	3.0 (5.9)	64	1.8 (5.1)	61	2.8 (5.0)
60 min	67	6.2 (9.4)	67	5.0 (9.9)	61	3.5 (5.6)
120 min	60	0.0 (1.9)	60	-2.0 (1.2)	58	-0.2 (1.6)
180 min	66	5.9 (8.3)	66	4.0 (7.0)	63	5.3 (8.2)
360 min	64	3.4 (5.4)	64	1.9 (5.1)	61	2.9 (5.7)

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.3.1 (API-E004-CL-B, Study Report), pg. 117 (Table 8-8)
Key: Δ=change compared to same-day baseline

In general, an increase in vital signs is noted after dosing, particularly early on (i.e., at 10 minutes), with return to baseline or close to baseline by 360 minutes. The magnitude mean change appears is balanced across treatment arms. Further analyses of the vital sign data from Trial B were performed as part of a consult review obtained from the Division of Cardiovascular and Renal Products (DCRP), which concluded that increases in systolic blood pressure and heart rate with high-dose epinephrine-HFA can be substantial in some patients (e.g., increases in heart rate, systolic blood pressure, and diastolic blood pressure of >60 bpm, > 50 mmHg, and >20 mmHg, respectively, in some patients), but that changes in blood pressure and heart rate expected with the proposed to-be-marketed dosage are modest. Conclusions from this consult review are

described in greater detail in Section 7.3.5, and vital sign data from Trials C and C2, which evaluated the to-be-marketed dose, are reviewed in Section 7.4.3.

4.4.3 Pharmacokinetics

A summary of pertinent pharmacokinetic data is provided in Section 4.4.2.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

A summary of the trials conducted in support of dose selection is provided in Section 3 of this review. The phase 3 development program conducted in support of epinephrine-HFA includes one 3-month efficacy and safety trial in adults and adolescents with a 3-month extension for safety (Trials C and C2), and a 4-week efficacy and safety study in pediatric patients 4 to 11 years of age (Trial D). A summary of these trials is provided in Table 4.

Table 4. Phase 3 Clinical Development Program

Trial *Year completed*	Design	N	Treatments	Duration	Primary Endpoint	Number of Sites *% of patients from US*
Adult and adolescent efficacy and safety trials						
API-E004-CL-C (Trial C) *2011*	R, DB or EB, PC, AC, PG	248 61 64	Epinephrine-HFA 2x125 mcg/inh QID Epinephrine-HFA Placebo-HFA QID Primatene® Mist 2x220 mcg/inh QID	12 weeks	AUC of Δ%FEV1	34 *100%*
API-E004-CL-C2 (Trial C2) Extension of Trial C *2012*	R, DB or EB, PC, AC, PG	134 38 35	Epinephrine-HFA 2x125 mcg/inh QID Epinephrine-HFA Placebo-HFA QID Primatene® Mist 2x220 mcg/inh QID	12 weeks	Safety	27 *100%*
Pediatric efficacy and safety trial (children ages 4-11 years)						

API-E004-CL-D (Trial D) *2012*	R, DB, PC, PG	35 35	Epinephrine-HFA 2x125 mcg/inh QID Epinephrine-HFA Placebo-HFA QID	4 weeks	AUC of Δ%FEV1	8 *100%*

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.2 (Tabular Listing of All Clinical Studies), pg. 5 (Table 5.2-1)
Note: N=number in ITT population randomized
Key: AC=active-controlled, DB=double-blind, EB=evaluator blind, PC=placebo-controlled, PG=parallel group, R=randomized

5.2 Review Strategy

The focus of this review is on the clinical development program conducted in support of epinephrine-HFA, which is proposed for use as a bronchodilator in patients with intermittent asthma. Data to support the selection of dose carried into the phase 3 program have already been reviewed in Section 4.4.2. The remainder of this clinical review addresses first the data presented in support of efficacy, and then the data in support of safety.

The review of efficacy focuses on the pivotal efficacy trial, Trial API-E004-CL-C (hereafter referred to as "Trial C"), a randomized, double-blind or evaluator-blind, placebo-controlled and active-controlled, parallel group trial with a 12-week treatment duration conducted in a population of adults and adolescents. The review of safety focuses on the premarket data, namely, the data provided by Trial C in combination with Trial API-E004-CL-C2 (hereafter referred to as "Trial C2"), which was a 12-week extension of Trial C. The Applicant also conducted a 4-week randomized, double-blind, placebo-controlled, parallel group efficacy and safety trial in pediatric patients ages 4 to 11 years (Trial API-E004-CL-D, hereafter referred to as "Trial D"). While the Applicant is not currently seeking approval for pediatric patients 4 to 11 years of age, FDA requested that the application include the available pediatric data for completeness, as there is concern that the proposed product may be used by consumers in this demographic group.

The general design of Trials C, C2, and D is presented in Section 5.3 of this review; a discussion of the efficacy data generated by these trials is provided in Section 6, and a discussion of the safety data in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

A summary of the protocols for the three phase 3 trials (Trials C, C2, and D) is provided here; the dose-ranging trials are discussed in Section 4.4.2.

Trial API-E004-CL-C (Trial C)

The administrative information and protocol for Trial C are presented below. This trial compared epinephrine-HFA 250 mcg (delivered as two 125 mcg inhalations) to placebo and to Primatene® Mist 440 mcg (delivered as two 220 mcg inhalations) in a population of adults and adolescents with asthma. Each treatment was administered four times daily for a total of 12 weeks.

The protocol for Trial C was amended once; the summary below is based on the final version of the protocol. A description of the changes provided by the protocol amendment follows the summary.

Administrative Information
Trial API-E004-CL-C (Trial C)

- Study Title: "A Randomized, Double- and Evaluator-Blinded, Active- and Placebo-Controlled, Three-Arm, Parallel, 12-Week Study in Adolescent and Adult Patients with Asthma."
- Study Dates: May 5, 2011 – November 16, 2011
- Study Sites: A total of 34 centers in the United States.
- Study Report Date: April 3, 2013

Objectives
Primary:

- To evaluate the efficacy and safety of epinephrine-HFA in adults and adolescents with asthma

Additional:

- To evaluate the functionality and reliability of the dose indicator and the performance of the product under routine use and cleaning

Design
This was a randomized, double-blind or evaluator-blind, placebo-controlled and active-controlled, parallel-group, multicenter trial.

The epinephrine-HFA and placebo treatments were double-blinded. Given the distinct appearance and cleaning requirements of the Primatene® Mist product, this treatment was evaluator-blinded only.

Treatments
Patients were randomized 4:1:1 to receive one of the following treatments:

- Epinephrine-HFA 250 mcg (delivered as two 125 mcg inhalations)
- Placebo
- Primatene® Mist 440 mcg (delivered as two 220 mg inhalations

Each treatment was administered four times daily for 12 weeks.

In addition, patients were provided albuterol for "as-needed" use.

Population
The protocol anticipated a sample size of approximately 300 total patients.

Key Inclusion Criteria:

- 12-75 years
- Documented asthma requiring inhaled epinephrine or β2-agonist, with or without inhaled corticosteroids (ICS), for at least 6 months
- Stable asthma disease, defined as no significant changes in therapy (with the exception of switching LABA to SABA, per the Investigator's discretion) and no asthma-related hospitalizations or emergency visits, for at least 4 weeks
- Can tolerate withholding treatment with inhaled bronchodilators and other allowed medications for the minimum washout periods described in Table 5
- Screening baseline FEV1 50-90% of predicted
- ≥12% airway reversibility after inhaling 440 mcg (delivered as two 220 mcg inhalations) of Primatene® Mist
- Females:
    - Of non-child bearing potential – OR –
    - Of children bearing potential, and not pregnant nor lactating, and agreed to use an acceptable method of contraception
- Demonstrating satisfactory technique in the use of MDIs and hand held PEF meter

Key Exclusion Criteria:

- Smoking history of ≥ 10 pack-years, or having smoked within 12 months
- Any current or past medical conditions that, per Investigator discretion, might affect responses to study medications, other than asthma
- Concurrent clinically significant disease
- Known intolerance or hypersensitivity to any component of the study medications
- Recent upper respiratory tract infection (within 2 weeks), or lower respiratory tract infection (within 4 weeks)
- Use of prohibited medications as described in Table 6
- Having been on other investigational trials in the last 30 days
- Known or highly suspected substance abuse

Table 5. Permitted medications (throughout trial), and required withholding times

Prohibited Medication Category	Withholding Time (prior to spirometry)
Epinephrine CFC-MDI	6 hours
Corticosteroids, inhaled, intranasal, or topical	6 hours
Mast cell stabilizers	6 hours
Oral and topical decongestants	8 hours
Antihistamines*	

Short-acting Long-acting	12 hours 24 hours
Leukotriene receptor antagonists	24 hours

Source: Applicant's NDS 205-920 Submission July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Protocol or Amendment), pg. 73 (Appendix II, Part 2)
Note: Withholding time is prior to spirometry at screening visit, and at Visits 1, 3, and 5
***With the exception of hydroxyzine, which was prohibited throughout**

Table 6. Prohibited medications (prior to screening and throughout trial), and associated washout intervals

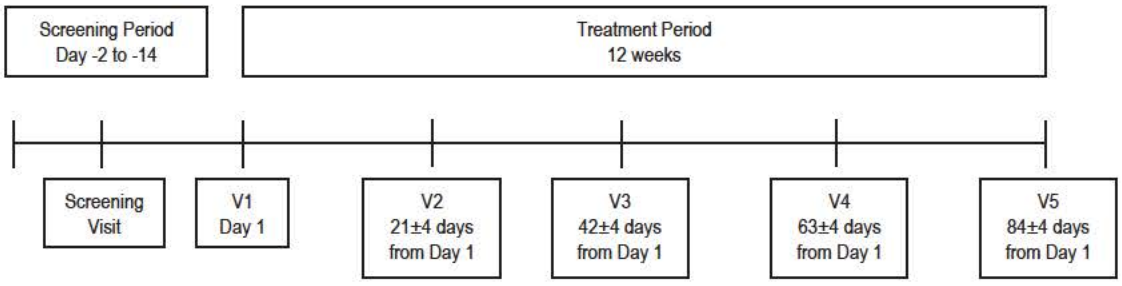
Prohibited Medication Category	Washout Interval
Corticosteroids, oral and parenteral	4 weeks
Anti-IgE	4 weeks
Monoamine Oxidase-A Inhibitors	2 weeks
Monoamine Oxidase-B Inhibitors	2 weeks
Tricyclic Antidepressants	2 weeks
Beta-blockers	2 weeks
Inhaled Anticholinergics*	2 weeks
Long-acting Beta-agonists (LABA), inhaled#	≥ 3-14 days
Beta-agonists, oral and parenteral	1 week
Theophyllines	1 week
Antihistamines with anticholinergic actions	5 days
Narcotic analgesics	24 hours for occasional use (chronic use prohibited)
Short-acting Beta-agonists (SABA), inhaled	8 hours^

Source: Applicant's NDA 205-920 Submission July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Protocol or Amendment), pg. 71-72 (Appendix II, Part I)
***Use of systemic anticholinergics for non-asthmatic indications was generally permitted, but subject to a 24 hour washout; use of topical ophthalmological anticholinergics was permitted**
#Patients on LABA were to be switched to SABA, with concomitant ICS, if applicable, at least 72 hours prior to Screening
^The washout interval was 1 hour in Trial C2.

Trial Conduct

The trial consisted of a screening visit (conducted 2 to 14 days prior to Day 1), and five visits during the 12-week treatment period. A trial schematic is presented in Figure 2.

Figure 2. Schematic, Trial C



Source: Generated by Reviewer

Priming, Dosing, and Cleaning Procedures:
A comparison of the priming, dosing, and cleaning procedures employed in Trial C for the epinephrine-HFA and Primatene® Mist devices is provided in Table 7.

Table 7. Priming, Dosing, and Cleaning Procedures, Trial C

	Epinephrine-HFA	Primatene® Mist
Priming	4 times prior to first dose; 2 times after two weeks of non-use	None
Dosing	Shake vigorously for several seconds immediately before each inhalation	No shaking required
Cleaning	Disassemble and clean daily, preferably after last evening dose to allow for air-drying time	Clean mouthpiece after each use

Spirometry:
As the Applicant is seeking an indication for the bronchodilator treatment of airflow obstruction in asthma, particular focus on the trial's spirometric assessments is warranted.

FEV1 maneuvers were conducted in general conformance with current American Thoracic Society (ATS) spirometry standards. FEV1 measurement acceptability criteria were adapted from ATS standards. FEV1 at each time point was tested with duplicate maneuvers, with an option for a 3rd maneuver if either of the first two attempts were unsuccessful; the highest value was used. Both pre- and post-bronchodilator spirometry was conducted at screening to determine eligibility. At Visits 1, 3, and 5, both pre-dose baseline and serial post-dose FEV1, at 5 (±2), 30 (±5), 60 (±10), 120 (±10), 180 (±15), 240 (±15), and 360 (±15) minutes, were conducted.

The full schedule of trial events is provided in Table 8.

Table 8. Schedule of Events, Trial C

	Screening Period	Treatment Period						
	Screening Visit	Daily Throughout	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	EW
	Day -2 to -14		Day 1	21 ± 4 days from Day 1	42 ± 4 days from Day 1	63 ± 4 days from Day 1	84 ± 4 days from Day 1	
Informed Consent	X							
Medical History and Demographics	X							
Verify Inclusion/Exclusion Criteria	X		X					
Medication History	X		X					
Physical Examination	X						X	X
Vital Signs	X		X*		X*		X*	X

12-lead ECG	X		X^				X^	
Serum Potassium and Glucose	X						X#	
PEF	X	X	X					
Screening Baseline FEV1	X							
Airway Reversibility Test	X							
Pregnancy Test	X						X	X
Clinical Laboratory Tests	X						X	X
MDI Training	X	X	X	X	X	X	X	
Serial FEV1			X		X		X	
Record Rescue Medication Use in eDiary		X						
Train, Dispense, Review Diary			X	X	X	X	X	
DASS, NAS	X	X						
Concomitant medication records /Queries	X		X	X	X	X	X	X
AE Query and Reporting	X		X	X	X	X	X	X
Device Cleaning		X						
Telephone Reminder@			X	X	X	X	X	X
Issue/Return/ Document Trial MDI			X	X	X	X	X	X
Visual Inspection, Documentation of Trial MDI Units			X	X	X	X	X	X
Dispense/ Document rescue MDI			X	X	X	X	X	X

Source: Applicant's NDA 205-920 Submission July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Protocol or Amendment), pg. 78 (Appendix VI)
Key: EW=early withdrawal
***At baseline, 2(±1), 10 (±3), 20 (±5), 60 (±10), and 360 (±15) minutes**
^At baseline, 2(±1), 10 (±3), 20 (±5), and 60 (±10), with additional follow-up if necessary
#At baseline, 15, and 120 minutes
@Telephone reminder of visits and visit restrictions, MDI cleaning, if deemed necessary by poor compliance

Asthma Exacerbations:

Asthma exacerbation was defined in this trial as follows:

- Significant worsening of clinical symptoms such as shortness of breath, chest tightness, wheezing, and cough, and
- Significant deterioration of PEF reading (e.g., 20% lower) personal best, or FEV1 (20% below screening baseline) if tested
- Worsening of symptoms and deterioration of PEF cannot be improved by the use of rescue MDI

Patients experiencing an asthma exacerbation during the trial were to be managed with rescue albuterol MDI, or with albuterol by nebulization, and/or ICS. Emergency visits to local medical facilities were permitted. Patients with severe, persistent, or repeated exacerbations, or those treated with prohibited medications, were to be withdrawn, at the discretion of the Investigator.

Endpoints

Primary Endpoint:

- Mean area under the curve (AUC) of ΔFEV1 (% change from same-day baseline FEV1) versus time ($AUC_{\Delta\%}$), at Study Visit-5 (Week 12)

Secondary Endpoints:

- AUC of FEV1 volume changes ($AUC_{\Delta v}$) versus time from the same-day baseline
- AUC of placebo-adjusted FEV1 % change from same-day baseline FEV1 versus time ($AUC_{\Delta\Delta\%}$)
- Curves of ΔFEV1%, ΔFEV1, and Δ placebo-adjusted FEV1% versus time
- Time to onset of bronchodilator effect (T_{onset}), determined by linear interpolation as the time point where FEV1 first reaches ≥12% over same-day baseline
- The peak bronchodilator response ($F_{Max)}$, defined as the maximum FEV1 increase (% change from Same-Day Baseline) post-dose
- The time to peak FEV1 effect (t_{Max}), defined as the time of F_{Max}
- Duration of bronchodilator effect ($t_{Duration}$), defined as the total length of time when FEV1 reaches and stays ≥12% above the respective same-day baseline values
- Percentage of positive responders (R%), including all subjects whose FEV1 exceed the same-day baseline by ≥12% within 30 minutes post-dose ("quick responders") , and during 6 hours post-dose ("overall responders")
- FEV1 at Visit 3 compared to Visits 1 and 5 (to evaluate efficacy over the life of the unit)
- Mean Daily Asthma Symptoms Scores (DASS) and Nighttime Awakening Scores (NAS)
- Mean daily morning pre-dose PEF

MDI Device and Dose Indicator Evaluations:

- MDI device functionality and in-use performance evaluations
  - Number and % of reported malfunctioning units in all returned study units that were demonstrated to have been properly cleaned and dried
  - Number and % of reported malfunctioning units in all returned study units that were not properly cleaned and dried
  - Subject compliance with the dosing and cleaning procedure
  - *In vitro* performance evaluations of the used study units
- Dose Indicator functionality and reliability evaluations
  - Number and % of subjects correctly switching to a new MDI inhaler
  - Concordance between E-diary recorded number of total actuations and that indicated by the Dose Indicator (i.e., number and % of actuation undercounting/overcounting)
  - Subject rating on comfort with use of unit and usefulness of indicator

Safety Evaluations

- Adverse events

- Vital signs
- 12-lead ECG
- Serum potassium and glucose, in addition to other clinical laboratory evaluations
- Rescue medication use
- Concomitant medications

Statistical Considerations

Analysis Population:

The primary population for all data analyses was specified in the protocol to be the Per Protocol Population (PPP), defined as patients who successfully completed 2 out of 3 clinical visits involving serial FEV1 measurement, and must have baseline and at least one of the two (5±2 and 30±5 minute) post-dose FEV1, and at least 5 out of 7 post-dose FEV1 data points, correctly measured for these two visits. The FEV1 data for pre-dose and 6 hours post-dose must also be available, and there must be no significant violations of the prohibited medications and required drug washout. The protocol also described a Treated Population (TP), defined as all patients who were randomized and took at least one dose of study medication. Safety evaluations were to be performed for the TP; additional efficacy evaluations would also be performed for the TP. In a subsequently submitted Statistical Analysis Plan (SAP), the primary population for efficacy analyses was changed to be the ITT Population, consistent with advice provided by the Agency.

Primary Efficacy Analysis:

The main analysis of the primary endpoint, mean area under the curve (AUC) of ΔFEV1 (% change from same-day baseline FEV1) versus time ($AUC_{\Delta\%}$), for the comparison of epinephrine-HFA to placebo, was prespecified to use Visit 5 data.

Interim Analysis:

No interim analysis was planned.

Protocol Amendment

The original protocol was submitted on March 10, 2011. A single protocol amendment was submitted to FDA on May 12, 2011. The changes provided by this amendment are reflected in the protocol description above, and included the following:

- The dose of epinephrine-HFA was changed from 90 mcg/inhalation to 125 mcg/inhalation; this amendment was made prior to the start of the trial
- Additional (earlier) time points were added to the evaluation of vital signs and ECGs

Trial API-E004-CL-C2 (Trial C2)

The administrative information and protocol for Trial C2 are presented below. This trial was a 3-month safety extension of Trial C.

The protocol for Trial C2 was amended once; the summary below is based on the final version of the protocol. A description of the changes provided by the protocol amendment follows the summary.

Administrative Information
Trial API-E004-CL-C2 (Trial C2)

- Study Title: "A 3-Month Safety Evaluation Extension to the 12-Week E004-C Study in Asthma Patients."
- Study Dates: November 9, 2011 – April 5, 2012
- Study Sites: A total of 27 centers in the United States.
- Study Report Date: April 3, 2013

Objectives
Primary:

- To assess the 6-month safety profile for epinephrine-HFA in adult and adolescent patients with asthma

Additional:

- To evaluate the performance of the MDI device under routine use and cleaning

Design
This was a randomized, double-blind or evaluator-blind, placebo-controlled and active-controlled, parallel-group, multicenter trial.

The epinephrine-HFA and placebo treatments were double-blinded. Given the distinct appearance and cleaning requirements of the Primatene® Mist product, this treatment was evaluator-blinded only.

The protocol specified that patients in the Primatene® Mist treatment arm of Trial C2 would be withdrawn from the trial at the first visit after the sunset date for this product (December 31, 2011).

Treatments
In the preceding trial (Trial C), patients were randomized 4:1:1 to receive one of the following treatments:

- Epinephrine-HFA 250 mcg (delivered as two 125 mcg inhalations)
- Placebo
- Primatene® Mist 440 mcg (delivered as two 220 mg inhalations

Patients enrolled in the extension Trial C2 were continued on the treatment to which they had been randomly assigned in Trial C. The treatment duration for epinephrine HFA and placebo was 3 months. The treatment duration for Primatene® Mist was variable, as patients in this treatment arm were withdrawn after the sunset date for this product.

In addition, patients were provided albuterol for "as-needed" use.

Population
The protocol anticipated a sample size of approximately 180 total patients (120 epinephrine-HFA, 30 placebo, 30 Primatene® Mist).

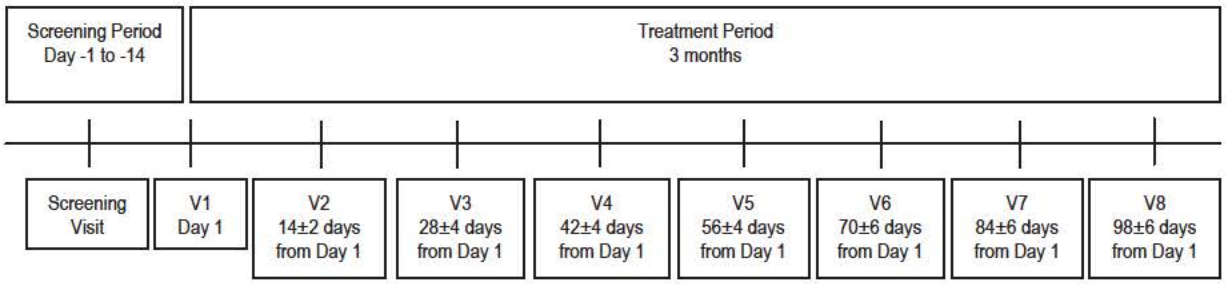
Key Inclusion Criteria:
The inclusion criteria for Trial C2 were the same as those for Trial C, with the following exceptions:

- Patients must have successfully completed Trial C within the last 135 days or be currently actively enrolled in Trial C
- Screening FEV1 and airway reversibility were not specified

Key Exclusion Criteria:
The exclusion criteria for Trial C2 were the same as those for Trial C. Both trials also generally had the same guidelines for prohibited medications (Table 6).

Trial Conduct
The trial consisted of a screening visit (conducted 1 to 14 days prior to Day 1), and eight visits during the 3-month treatment period. A trial schematic is presented in Figure 2.

Figure 3. Schematic, Trial C2



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Priming, Dosing, and Cleaning Procedures:
The priming, dosing, and cleaning procedures for Trial C2 were the same as those for Trial C (see Table 7), with the exception that it omitted the instruction to prime twice after a period of non-use two weeks or longer.
The full schedule of trial events is provided in Table 9.

Table 9. Schedule of Events, Trial C2

	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	EW

	Visit									
	D -2 to -14	D1	21 ± 4 days from D1	42 ± 4 days from D1	63 ± 4 days from D1	84 ± 4 days from D1	84 ± 4 days from D1	84 ± 4 days from D1	98 ± 6 days from D1	
Informed Consent	X									
Medical History and Demographics	X									
Verify Inclusion/Exclusion Criteria	X	X								
Medication History	X	X								
Physical Examination	X								X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X				X				X	*
Pregnancy Test	X								X	X
Clinical Laboratory Tests	X								X	X
Serum Potassium and Glucose	X								X	
MDI Training, etc.	X									
Train, Dispense, Review Diary		X	X	X	X	X	X	X	X	
Record Rescue Medication Use in Diary	X	X	X	X	X	X	X	X	X	X
PEF		X	X	X	X	X	X	X	X	
DASS, NAS		X	X	X	X	X	X	X	X	
Concomitant medication records /Queries	X	X	X	X	X	X	X	X	X	X
AE Query and Reporting	X	X	X	X	X	X	X	X	X	X
Device Cleaning		X	X	X	X	X	X	X	X	
Issue/Return/ Document Trial MDI		X	X	X	X	X	X	X	X	
Visual Inspection, Documentation of Trial MDI Units		X	X	X	X	X	X	X	X	

Source: Applicant's NDA 205-920 Submission July 22, 2013, Section 5.3.5.1 (API-E004-CL-C2, Protocol or Amendment), pg. 48 (Appendix V)
Key: D=day; EW=early withdrawal
*If needed

Asthma Exacerbations:

The definition of asthma exacerbation in Trial C2 was the same as that for Trial C. The management of patients with asthma exacerbation, including the guidelines for withdrawal, was also the same for both trials.

Endpoints

There were no efficacy assessments in this safety-focused trial. Safety evaluations conducted in the trial are described below. In addition to the evaluation of safety, the trial included an evaluation of devices that were reported as malfunctioning.

Safety Evaluations

- Adverse events
- Vital signs
- 12-lead ECG

- Serum potassium and glucose, in addition to other clinical laboratory evaluations
- Rescue medication use
- Concomitant medications

Statistical Considerations

Analysis Population:

As was the case for Trial C, the primary population for all safety analyses was specified to be the Treated Population (TP), defined as all patients who were randomized and took at least one dose of study medication.

Interim Analysis:

No interim analysis was planned.

Protocol Amendment

The original protocol was submitted on October 12, 2011. A single protocol amendment was submitted to FDA on November 8, 2011. The changes provided by this amendment are reflected in the protocol description above, and included the following:

- The duration of the permitted interval between Trials C and C2 was increased from 90 days to 135 days.
- The washout interval for SABA was changed from 8 hours to 1 hour

Trial API-E004-CL-D (Trial D)

The administrative information and protocol for Trial D are presented below. This trial compared epinephrine-HFA 250 mcg (delivered as two 125 mcg inhalations) to placebo in a population of children ages 4 to 11 with asthma. Each treatment was administered four times daily for a total of 4 weeks.

The protocol for Trial D was amended once; the summary below is based on the final version of the protocol. A description of the changes provided by the protocol amendment follows the summary.

Administrative Information

Trial API-E004-CL-D (Trial D)

- Study Title: "A Randomized, Double-Blind, Placebo-Controlled, Two-Arm, Parallel, 4-Week in 4-11 Year Old Children with Asthma."
- Study Dates: October 8, 2011 – March 14, 2012
- Study Sites: A total of 8 centers in the United States.
- Study Report Date: April 3, 2013

Objectives

Primary:

- To evaluate the efficacy and safety of epinephrine-HFA in pediatric patients 4-11 years of age with asthma

Additional:

- To evaluate the functionality and reliability of the dose indicator and the performance of the product under routine use and cleaning

Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial.

Treatments

Patients were randomized 1:1 to receive one of the following treatments:

- Epinephrine-HFA 250 mcg (delivered as two 125 mcg inhalations)
- Placebo

Each treatment was administered four times daily for 4 weeks.

In addition, patients were provided albuterol for "as-needed" use.

Population

The protocol anticipated a sample size of approximately 60 total patients, stratified by age (equal numbers of patients ages 4-8 and 9-11).

Key Inclusion Criteria:

- Generally healthy male, and premenarchal female, ages 4-11 years
- Documented asthma requiring inhaled epinephrine or β2-agonist, with or without inhaled corticosteroids (ICS), for at least 6 months
- Capable of performing spirometry
- Stable asthma disease, defined as no significant changes in therapy (with the exception of switching LABA to SABA, per the Investigator's discretion) and no asthma-related hospitalizations or emergency visits, for at least 4 weeks
- Can tolerate withholding treatment with inhaled bronchodilators and other allowed medications for the minimum washout periods described in Table 5
- Screening baseline FEV1 50-90% of predicted
- ≥12% airway reversibility after inhaling 440 mcg (delivered as two 220 mcg inhalations) of Primatene® Mist
- Demonstrating satisfactory technique in the use of MDIs and hand held PEF meter

Key Exclusion Criteria:

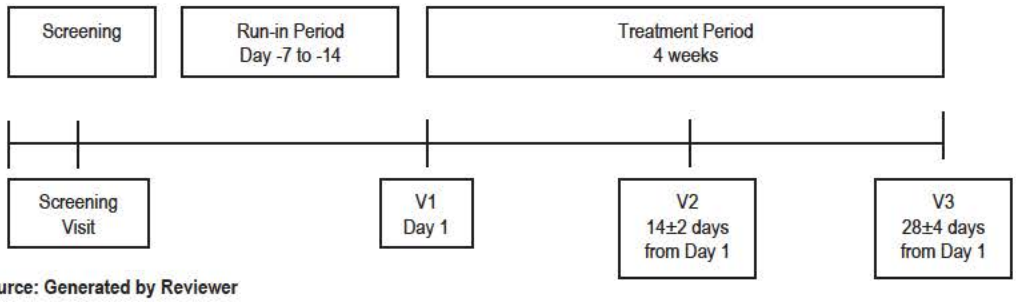
- Any current or past medical conditions that, per Investigator discretion, might affect responses to study medications, other than asthma
- Concurrent clinically significant disease
- Known intolerance or hypersensitivity to any component of the study medications

- Recent upper respiratory tract infection (within 2 weeks), or lower respiratory tract infection (within 4 weeks)
- Use of prohibited medications as described in Table 6
- Having been on other investigational trials in the last 30 days

Trial Conduct
The trial consisted of a screening visit (conducted 7 to 14 days prior to Day 1), a run-in period of 7-14 days, and a 4-week treatment period with three visits. During the run-in period, patients were maintained on their current inhaled SABA, and all patients on LABA were switched to SABA (e.g. Primatene® Mist or albuterol MDI), with concomitant ICS, if applicable.

A trial schematic is presented in Figure 4.

Figure 4. Schematic, Trial D



Source: Generated by Reviewer

Priming, Dosing, and Cleaning Procedures:
The priming, dosing, and clearing procedures for the epinephrine-HFA device in Trial D were the same as those for employed in Trial C (see Table 7).

Spirometry:
FEV1 maneuvers were conducted in general conformance with current American Thoracic Society (ATS) spirometry standards. FEV1 measurement acceptability criteria were adapted from ATS standards. FEV1 at each time point was tested with duplicate maneuvers, with an option for a 3rd maneuver if either of the first two attempts were unsuccessful; the highest value was used. Both pre- and post-bronchodilator spirometry was conducted at screening to determine eligibility. At Visits 1 and 3 both pre-dose baseline and serial post-dose FEV1, at 5 (±2), 30 (±5), 60 (±10), 120 (±10), 180 (±15), 240 (±15), and 360 (±15) minutes, were conducted.

The full schedule of trial events is provided in Table 10.

Table 10. Schedule of Events, Trial D

	Screening Period	Treatment Period

	Screening Visit	Visit 1	Visit 2	Visit 3	EW
	Day -7 to -14	Day 1	14 ± 2 days from Day 1	28 ± 4 days from Day 1	
Informed Consent	X				
Medical History and Demographics	X				
Verify Inclusion/Exclusion Criteria	X				
Medication History	X				
Physical Examination	X			X	X
Vital Signs	X	X*		X*	X
12-lead ECG	X	X@		X@	
Serum Potassium and Glucose	X			X#	
Screening Baseline FEV1	X				
Airway Reversibility Test	X				
Clinical Laboratory Tests	X			X	X
MDI Training	X	X	X	X	
Serial FEV1		X^		X^	
Record Rescue Medication Use in Diary		X	X	X	
Train, Dispense, Review Diary		X	X	X	
PEF	X	X	X	X	
DASS, NAS	X	X	X	X	
Concomitant medication records /Queries	X	X	X	X	X
AE Query and Reporting	X	X	X	X	X
Device Cleaning		X			
Issue/Return/ Document Trial MDI		X	X	X	
Visual Inspection, Documentation of Trial MDI Units		X	X	X	
Evaluate Patient's Use of Dose Indicator		X	X	X	
Dispense/ Document rescue MDI		X	X	X	

Source: Applicant's NDA 205-920 Submission July 22, 2013, Section 5.3.5.1 (API-E004-CL-D, Protocol or Amendment), pg. 59 (Appendix VI)
Key: EW=early withdrawal
*At baseline, 3(±2), 20(±5), 60(±10), and 360(±15) minutes
@At baseline, 3(±2), 20(±5), 60(±10) minutes, and additional, if necessary
#At baseline, 15(±5), and 120(±20) minutes
^At baseline, 5(±2), 30(±5), 60(±10), 120(±10), 180(±15), 240(±15), 360(±15) minutes

Asthma Exacerbations:

The definition of asthma exacerbation in Trial D was the same as that for Trials C and C2. The management of patients with asthma exacerbation, including the guidelines for withdrawal, was also the same for both trials.

Endpoints

Primary Endpoint:

- Area under the curve (AUC) of FEV1's relative change (from same-day baseline) versus time, i.e., AUC of ΔFEV1%, at Study Visit-3 (Week 4)

Secondary Endpoints:

- AUC of FEV1 volume changes (AUC of ΔFEV1)
- Maximum of ΔFEV1% (F_{max})
- Curves of ΔFEV1, and ΔFEV1%, versus time
- Time to onset of bronchodilator effect (T_{onset}), determined by the time point (within 60 minutes) where FEV1 first reaches ≥12% above same-day baseline
- Time to peak FEV1 effect (t_{max}), defined as the time of F_{max}
- Duration of efficacy ($t_{duration}$), defined as the total length of time when ΔFEV1% reaches and stays ≥12% above same-day baseline
- Percentage of positive responders (R%), including all subjects whose F_{max} reaches ≥12% above same-day baseline
- Mean DASS
- Mean daily NAS
- Mean daily morning pre-dose PEF

MDI Device and Dose Indicator Evaluations:

- MDI device functionality and in-use performance evaluations
  - Number and % of reported malfunctioning units in all returned study units
- Dose Indicator functionality and reliability evaluations
  - At Visits 2 and 3: number and % of subjects correctly reading and interpreting the status of inhaler usage from the dose indicator
  - At Visit 3: subject rating on comfort with use of unit and usefulness of indicator

Safety Evaluations

- Adverse events
- Vital signs
- 12-lead ECG
- Serum potassium and glucose, in addition to other clinical laboratory evaluations
- Rescue medication use
- Concomitant medications

Statistical Considerations

Analyses Populations:

The primary efficacy analysis was to be conducted for both the Intent-to-Treat (ITT) population and the Per Protocol Population (PPP). The ITT population is defined as all randomized patients who have passed enrollment confirmation at Visit 1. The PPP is defined as patients with a valid pre-dose baseline FEV1, who have correctly taken randomized study treatment, and who have at least 2 of 3 post-dose serial FEV1

measurements at 5, 30, and 60 minutes, and have at least 5 of all 7 post-dose serial FEV1 data points.

The protocol also described a Treated Population (TP), defined as all patients who were randomized and took at least one dose of study medication. Safety evaluations were to be performed for the TP; additional efficacy evaluations would also be performed for the TP.

Primary Efficacy Analysis:
The main analysis of the primary endpoint, AUC of ΔFEV1%, for the comparison of epinephrine-HFA to placebo, was prespecified to use Visit 5 data.

Interim Analysis:
No interim analysis was planned.

Protocol Amendment
The original protocol was submitted on August 15, 2011. A single protocol amendment was submitted to FDA on September 28, 2011. The changes provided by this amendment are reflected in the protocol description above, and included the following:

- PEF was replaced by FEV1 as the primary efficacy endpoint for children 4 to 5 years of age
- An analysis of efficacy using the ITT population was added to the already planned analysis using the PPP.

6 Review of Efficacy

Efficacy Summary

The Applicant proposes epinephrine-HFA for OTC marketing for the "temporary relief of mild symptoms of intermittent asthma in adults and adolescents 12 years of age and older." Evidence of efficacy comes primarily from Trial C, a randomized, double-blind or evaluator-blind, placebo-controlled and active-controlled, parallel group trial with a 12-week treatment duration conducted in a population of adults and adolescents. This trial compared epinephrine-HFA at the maximum to-be-marketed dose (two 125 mcg inhalations), to both placebo and the reference product, Primatene® Mist (two 220 mcg inhalations). All of the treatments were administered on a regular schedule, four times daily, for 12 weeks. Trial C included patients with stable asthma disease requiring use of inhaled epinephrine or β-2 agonist, with or without inhaled corticosteroids, for at least 6 months. Patients were required to demonstrate reversibility at baseline, and had a mean baseline FEV1 of 2.3 L.

The primary efficacy endpoint in Trial C was mean area under the curve (AUC) of ΔFEV1 (% change from same-day baseline FEV1) versus time ($AUC_{\Delta\%}$), at study Visit 5 (Week 12); the Applicant's abbreviation for the primary endpoint is $AUC_{0\text{-}6hr}$ of Δ%FEV1, and is expressed in units of $\%^{x}hr$. Results for the primary endpoint demonstrate statistical significance for the comparison between epinephrine-HFA and placebo, and are robust to the various methods of missing data handling and population definitions. Results for Primatene® Mist are also statistically significant, with a magnitude of effect that is similar to that demonstrated for epinephrine-HFA.

The results for additional spirometric endpoints, including serial FEV1 (L) from baseline to 360 minutes post-dose, at the start and end of treatment in Trial C (i.e., Day 1 and Week 12), were supportive of the primary endpoint. Spirometry is an appropriate choice of endpoint for a purported bronchodilator, and the magnitude of effect demonstrated for epinephrine-HFA is likely to be clinically meaningful. Taken together, these data provide evidence of epinephrine-HFA's efficacy as a bronchodilator.

In addition to Trial C, the Applicant also conducted a 4-week randomized, double-blind, placebo-controlled, parallel group efficacy and safety trial in pediatric patients ages 4 to 11 years (Trial D), which also evaluated $AUC_{0\text{-}6hr}$ of Δ%FEV1 as the primary endpoint. In contrast to the results for adults and adolescents in Trial C, the results for the analysis of the primary endpoint in Trial D did not demonstrate statistical significance. It should be noted that the Applicant is not currently seeking approval for this age group. A second pediatric efficacy and safety trial, API-E004-CL-D2 (Trial D2), was initiated in November 2012 and is currently in process.

6.1 Indication

The Applicant proposes epinephrine-HFA for OTC marketing for the "temporary relief of mild symptoms of intermittent asthma in adults and adolescents 12 years of age and older." The wording of this indication is consistent with the currently effective monograph for cough, cold, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter use.[18] The proposed age range of 12 years and older is narrower than that of the discontinued Primatene® Mist product, which was indicated down to 4 years of age.

6.1.1 Methods

Refer to Section 5.3 for a discussion of the general design of the efficacy trial in adults and adolescents (Trial C) and the efficacy trial in pediatric patients 4 to 11 years of age (Trial D).

[18] 21 CFR 341.76

6.1.2 Demographics

Adults and Adolescents 12 years of age and older

Demographic and other baseline characteristics of patients in Trial C are provided in Table 11, and asthma disease characteristics for this population are provided in Table 12. While the available data does not allow for a complete assessment of patients' asthma severity, the data for FEV1 %predicted indicate that at least some patients might be classified as having persistent asthma according to the 2007 NAEPP EPR3.[19]

Table 11. Demographic and Other Baseline Characteristics of the Treated Population, Trial C

	Placebo N=61	Epinephrine-HFA N=248	Primatene® Mist N=64
Age (years)			
Mean ± SD	40 ± 14	39 ± 15	41 ± 16
Range	13-69	12-75	13-71
Gender			
Female, n (%)	40 (66)	149 (60)	35 (55)
Race			
Caucasian, n (%)	40 (66)	177 (71)	49 (77)
African American, n (%)	14 (23)	39 (16)	9 (14)
Hispanic/Latino, n (%)	4 (7)	23 (9)	5 (8)
Asian, n (%)	1 (2)	2 (1)	1 (2)
Other, n (%)	2 (3)	7 (3)	0 (0)
Weight (Kg)			
Mean ± SD	82 ± 20	84 ± 20	83 ± 24
Height (cm)			
Mean ± SD	167 ± 11	169 ± 9	169 ± 11

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Study Report), pg. 109 (Table 7.2-1)
Note: N=Number of patients in the ITT

Table 12. Asthma Disease Characteristics of the Treated Population, Trial C

	Placebo N=61	Epinephrine-HFA N=248	Primatene® Mist N=64
FEV1 (L) at Screening			
Mean ± SD	2.3 ± 0.6	2.3 ± 0.6	2.3 ± 0.6
Median	2.2	2.3	2.3
Range	1.3, 4.1	1.1, 4.5	1.1, 4.1

[19] 2007 NHLBI National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3, pg. 74 (Figure 3-4c).

FEV1 %predicted at Screening			
< 80%, n (%)	52 (85)	213 (86)	52 (81)
≥ 80%, n (%)	9 (15)	35 (14)	12 (19)
% Reversibility			
Mean ± SD	18.2 ± 5.9	21.2 ± 11.1	20.4 ± 10.1
Median	16.4	17.6	17.8
Range	12.0, 36.0	9.2, 86.9	9.0, 66.2
ICS user at Screening			
ICS user, n (%)	31 (50.8)	122 (49.2)	40 (62.5)
ICS non-user, n (%)	30 (49.2)	126 (50.8)	24 (37.5)

Source: Applicant's NDA 205-920 Submission dated December 20, 2013, Section 1.2 (Cover Letters), pg. 19 (Table H)
Note: N=Number of patients in the Treated Population

Demographic and other baseline characteristics were generally well-balanced across treatment arms. While the majority of patients were Caucasian, a substantial proportion was of other races/ethnicities. Asthma disease characteristics were also generally balanced across treatment arms, with the exception of the percentage of patients reported to be ICS users at screening, which was higher for patients in the Primatene® Mist treatment arm compared to the other two treatment arms. Details of smoking history are not provided as these data were not collected; the protocol for Trial C did specify, however, the exclusion of patients with a smoking history greater than or equal to 10 pack-years, or with a history of smoking within the past 12 months.

Children 4 to 11 years of age

Demographic and other baseline characteristics of patients in Trial D are provided in Table 13.

Table 13. Demographic and Other Baseline Characteristics of the Treated Population, Trial D

	Placebo N=35	Epinephrine-HFA N=35
Age (years)		
Mean ± SD	8 ± 2	9 ± 2
Range	4-11	4-11
Gender		
Female, n (%)	11 (31)	15 (43)
Race		
Caucasian, n (%)	14 (40)	15 (43)
African American, n (%)	11 (31)	11 (31)
Hispanic/Latino, n (%)	9 (26)	8 (23)
Other, n (%)	1 (3)	1 (3)
Weight (Kg)		

Mean ± SD	35 ± 15	37 ± 18
Height (cm)		
Mean ± SD	132 ± 13	135 ± 16

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-D, Study Report), pg. 102 (Table 7-4),
Note: N=Number of patients in the ITT

Demographic and other baseline characteristics were well-balanced across treatment arms.

6.1.3 Subject Disposition

Adults and Adolescents 12 years of age and older
The disposition of the patients participating in Trial C is provided in Table 14.

Table 14. Subject Disposition for Trial C

	Placebo	Epineprhine-HFA	Primatene®
Randomized	**Number of Patients**		
	61	248	64
Intent-To-Treat	**Number of Patients (% Randomized)**		
	61 (100)	248 (100)	64 (100)
Disposition	**Number of Patients (% ITT)**		
Completion Status			
Discontinued/Missed Treatment*	5 (8)	33 (13)	9 (14)
Reason for Discontinuation			
Personal/ Withdrew consent	0	8 (3)	3 (5)
Lost to follow-up	2 (3)	2 (1)	1 (2)
Protocol Violation	0	6 (2)	2 (3)
Adverse event	3 (5)	17 (7)	3 (5)

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Study Report), pg. 98 (Table 6.1-3, Table 6.1-4)
*At Visit 5

The percentage of patients who withdrew from Trial C was somewhat higher for the active treatment arms (13% and 14% for epinephrine-HFA and Primatene® Mist, respectively) compared to placebo (8%), but withdrawals due to adverse events were generally balanced (5-7%) across all arms. Further details on adverse events leading to withdrawal are provided in Section 7.3.3.

Children 4 to 11 years of age
The disposition of the patients participating in Trial D is provided in Table 15.

Table 15. Subject Disposition for Trial D

	Placebo	Epinephrine-HFA
Randomized	**Number of Patients**	
	35	35
Intent-To-Treat	**Number of Patients (% Randomized)**	
	35 (100)	35 (100)
Disposition	**Number of Patients (% ITT)**	
Completion Status		
Discontinued/Missed Treatment*	3 (9)	4 (11)
Reason for Discontinuation		
Personal/ Withdrew consent	1 (3)	0
Protocol Violation	0	2 (6)
Adverse event	2 (6)	2 (6)

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-D, Study Report), pg. 76 (Table 6-2), 84 (Table 7-1)
***Before treatment at Visit 3**

The percentage of patients who withdrew from Trial D was balanced across treatment arms.

6.1.4 Analysis of Primary Endpoint(s)

Adults and Adolescents 12 years of age and older

The primary efficacy endpoint in the single efficacy trial for adults and adolescents (Trial C) was Mean area under the curve (AUC) of ΔFEV1 (% change from same-day baseline FEV1) versus time ($AUC_{\Delta\%}$), at study Visit 5 (Week 12); the Applicant's abbreviation for the primary endpoint is **$AUC_{0\text{-}6hr}$ of Δ%FEV1**, and is expressed in units of %^{x}hr. Spirometry is an appropriate choice of endpoint for a purported bronchodilator. The clinical development program also included other spirometric-related endpoints (e.g., peak bronchodilator effect, time to onset, etc.), which are discussed in Section 6.1.5. These additional data are important for providing a more complete assessment of epinephrine-HFA's bronchodilatory action.

The Application includes results from four types of efficacy analyses: three for the ITT population, which utilized different approaches to the handling of missing data (Model A ["Closest Data Model"], Model B ["Placebo Model"], and Model C ["Baseline Model"]), and one for the PPP. Of these four approaches, the Applicant proposed Model A as the primary analysis, whereas the FDA statistical review identified Model C as the preferred approach. Model A imputes missing data based on measurements from a previous visit or from the group mean of the same arm at the same visit from the per protocol population, relying on the assumption that the data are missing at random. Model C imputes missing data with the patient's baseline score, and generally provides a conservative point estimate of the treatment effect. Results for the primary efficacy endpoint from Trial C, using both the Applicant's primary analysis (Model A) and FDA's

preferred approach (Model C), are provided in Table 16. The p-values in Table 16 are for the comparison to placebo, and are based on two-sided t-tests.

Table 16. Results for the Primary Endpoint, $AUC_{0\text{-}6hr}$ of Δ%FEV1 (%ˣhr), at Week 12, Trial C

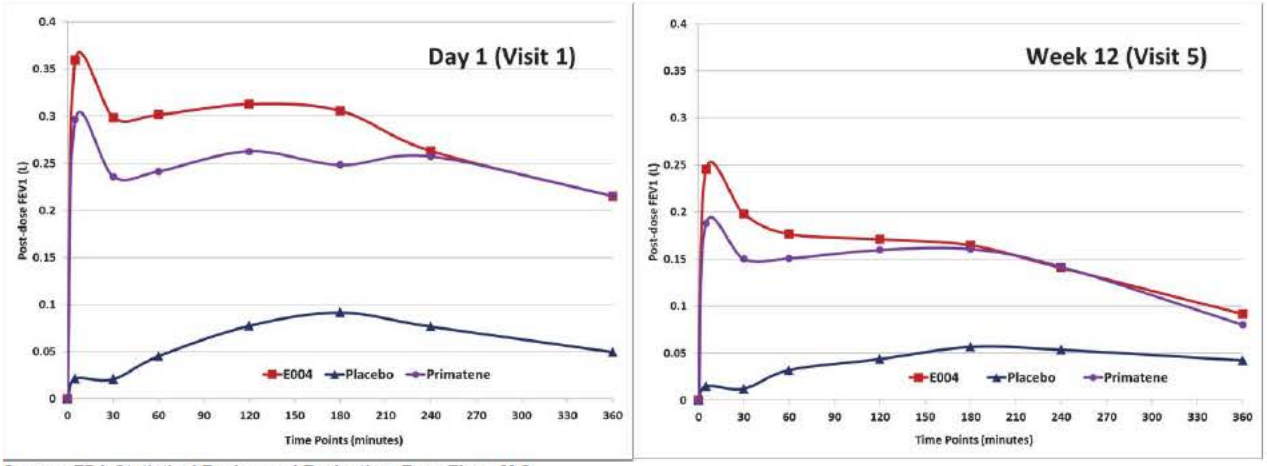
	ITT	Model A		Model C	
Treatment Arm	**N**	**Mean *(SD)***	**p-value**	**Mean *(SD)***	**p-value**
Epinephrine-HFA	248	47.3 *(54.2)*	<0.0001	40.6 *(56.1)*	0.0007
Primatene® Mist	64	41.0 *(43.4)*	0.0038	35.7 *(45.7)*	0.014
Placebo	61	14.6 *(55.6)*	--	12.8 *(55.8)*	--

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Study Report), pg. 123 (Table 7.4-2)

Results for the primary endpoint demonstrate statistical significance for the comparison between epinephrine-HFA and placebo, and are robust to the various methods of missing data handling and population definitions. Results for Primatene® Mist are also statistically significant, with a magnitude of effect that is similar to that demonstrated for epinephrine-HFA.

Although the original NDA included mean Δ%FEV1, it did not include data for mean FEV1 over time. This was requested by FDA and received in a submission dated November 5, 2013. Serial FEV1 (L), from baseline to 360 minutes post-dose, at the start and end of treatment in Trial C (i.e., Day 1 and Week 12), are presented in Figure 5.

Figure 5. Serial FEV1, 0-360 minutes post-dose on Day 1 and Week 12, Trial C, ITT Population (Model C)



Source: FDA Statistical Review and Evaluation, Feng Zhou, M.S.

The curves for FEV1 demonstrate a separation between epinephrine-HFA and placebo at each time point on both Day 1 and Week 12, although the degree of separation is less at the end of treatment compared to the start of treatment. The effect of epinephrine-HFA appears to be greater than Primatene® Mist at some time points, particularly early on. These data are supportive of the findings for the primary endpoint, and the magnitude of effect demonstrated for epinephrine-HFA is likely to be clinically meaningful..

In addition to the request for mean FEV1 over time, the FDA also requested that the Applicant submit data for $AUC_{0\text{-}6hr}$ of FEV1, F_{max} of FEV1, and T_{max} of FEV1. These data were submitted by the Applicant on November 5, 2013. Results for these additional secondary endpoints (Model A and Model C analyses), along with those for one further endpoint (change in FEV1 at 5 minutes post-dose) evaluated by the FDA statistical reviewer, are provided in Table 17. The p-values are for the comparison to placebo, and are based on two-sided t-tests.

Table 17. Results for the Additional Secondary Endpoints, Trial C, ITT Population

Treatment Arm	N	Model A		Model C	
		Mean *(SD)*	p-value	Mean *(SD)*	p-value
$AUC_{0\text{-}6hr}$ of FEV1 *($L^x hr$)*					
Epinephrine-HFA	248	15.8 *(3.9)*	0.0082	15.6 *(4.0)*	0.0217
Primatene® Mist	64	15.7 *(4.2)*	0.0656	15.4 *(4.0)*	0.1282
Placebo	61	14.4 *(3.6)*	--	14.4 *(3.6)*	--
Peak Bronchodilator Effect (F_{Max}) of FEV1 *(L)*					
Epinephrine-HFA	248	2.8 *(0.7)*	0.0028	2.7 *(0.7)*	0.0161
Primatene® Mist	64	2.8 *(0.7)*	0.0649	2.7 *(0.7)*	0.1589
Placebo	61	2.5 *(0.6)*	--	2.5 *(0.6)*	--
Time to Peak Bronchodilator Effect (t_{Max}) of FEV1 *(hours)*					
Epinephrine-HFA	248	1.2 *(1.6)*	<0.0001	1.0 *(1.4)*	0.0018
Primatene® Mist	64	1.4 *(1.7)*	0.002	1.2 *(1.7)*	0.0268
Placebo	61	2.5 *(2.1)*	--	2.0 *(2.1)*	--

ΔFEV1 at 5 minutes post-dose (L)					
Epinephrine-HFA	248	0.29 *(0.22)*	<0.05	0.25 *(0.24)*	<0.05
Primatene® Mist	64	0.23 *(0.21)*	--*	0.19 *(0.23)*	--*
Placebo	61	0.02 *(0.14)*	--	0.02 *(0.14)*	--

Source: Applicant's NDA 205-920 Submission dated November 5, 2013, Section 1.2 (Cover Letter), pg. 6 (Table 7.4-2S); FDA Statistical Review and Evaluation, Feng Zhou, M.S.
*** The FDA evaluation of ΔFEV1 at 5 minutes post-dose includes a p-value for the comparison between epinephrine-HFA and placebo, but not for the comparison between Primatene® Mist and placebo**

Results for these additional secondary endpoints demonstrate statistical significance for the comparison between epinephrine-HFA and placebo, and are robust to the various methods of missing data handling. Results for Primatene® Mist, in general, did not demonstrate statistical significance. These data are supportive of the findings for the primary endpoint.

Children 4 to 11 years of age

The Applicant is not currently seeking approval for pediatric patients 4 to 11 years of age. Nevertheless, FDA requested that the application include the available pediatric data for completeness, as the epinephrine-CFC-MDI product was approved down to 4 years of age and there is concern that the proposed product may be used by consumers in this demographic group.

The primary efficacy endpoint in the single efficacy trial for children 4 to 11 years of age (Trial D) was the same as that evaluated in Trial C: $AUC_{0\text{-}6hr}$ of Δ%FEV1. The Applicant's analysis of the primary endpoint was conducted using a per protocol population (PPP). Of the 70 patients in the ITT population, 25 were disqualified (12 patients in the epinephrine-HFA treatment arm and 13 patients in the placebo arm) and therefore not included in the PPP; these disqualifications were largely due to missing or inadequate FEV1 data. Results for the primary endpoint from Trial D are provided in Table 18. The Applicant's analysis using the PPP is presented, along with an ITT analysis (using a Model C approach to missing data) conducted by the FDA statistical reviewer.

Table 18. Results for the Primary Endpoint, AUC0-6hr of Δ%FEV1 (%xhr), at Week 4, Trial D

	ITT	Model C		PPP		
Treatment Arm	**N**	**Mean *(SD)***	**p-value**	**N**	**Mean *(SD)***	**p-value**
Epinephrine-HFA	35	34.15 *(60.29)*	0.124	23	47.6 *(68.6)*	0.125*

Placebo	35	15.79 *(34.63)*	--	22	21.2 *(41.5)*	--

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-D, Study Report), pg. 109 (Table 7-8); FDA Statistical Review and Evaluation, Feng Zhou, M.S.
*** p-value is based on a two-sided t-test as reported in the FDA statistical review; the Applicant's analysis reported a one-sided p-value**

In both the Applicant's PPP analysis and FDA's ITT analysis the results for the primary endpoint fail to demonstrate statistical significance. The Applicant suggests that these data may be limited by the small sample size and, potentially, a shorter efficacy duration for children compared to adults. The former issue may be addressed by an adequately designed and conducted pediatric efficacy trial that provides high-quality spirometric data. The latter issue is hypothetical and needs further data for verification.

Given the failure of the primary endpoint to demonstrate statistical significance, no further efficacy results from Trial D are discussed in this review. Additional results are described in FDA's Statistical Review and Evaluation. A second pediatric efficacy and safety trial (API-E004-CL-D2 or Trial D2) was initiated in November 2012 and is currently in process.

6.1.5 Analysis of Secondary Endpoints(s)

Adults and Adolescents 12 years of age and older
Applicant evaluated a number of secondary endpoints in Trial C; however, no adjustment for multiplicity was performed, so the p-values presented below are nominal values. Results for selected secondary endpoints (Model A and Model C analyses) are provided in Table 19. The p-values are for the comparison to placebo, and are based on two-sided t-tests.

Table 19. Results for the Selected Endpoints, Trial C, ITT Population

Treatment Arm	N	Model A		Model C	
		Mean *(SD)*	p-value	Mean *(SD)*	p-value
$AUC_{0\text{-}6hr}$ of ΔFEV1 *($L^{x}hr$)*					
Epinephrine-HFA	248	1.08 *(1.15)*	<0.0001	0.92 *(1.20)*	0.0005
Primatene® Mist	64	0.97 *(1.08)*	0.0024	0.84 *(1.14)*	0.009
Placebo	61	0.3 (1.31)	--	0.26 *(1.32)*	--
Time to onset (T_{Onset}) *(minutes)*					
Epinephrine-HFA	248	16.0 *(46.1)*	0.0038	18.2 *(50.7)*	0.0047

Primatene® Mist	64	42.3 *(68.0)*	0.047	40.1 *(66.2)*	0.040
Placebo	61	99.1 *(100.9)*	--	99.1 *(100.9)*	--
Peak Bronchodilator Effect (F_{Max}) of Δ%FEV1 *(%)*					
Epinephrine-HFA	248	15.4 *(11.4)*	<0.0001	13.2 *(11.4)*	0.0016
Primatene® Mist	64	13.0 *(8.1)*	0.012	11.5 *(9.4)*	0.088
Placebo	61	8.9 *(9.8)*	--	8.5 *(10.1)*	--
Time to Peak Bronchodilator Effect (t_{Max}) Δ%FEV1 *(hours)*					
Epinephrine-HFA	248	1.17 *(1.57)*	<0.0001	1.02 *(1.43)*	0.0018
Primatene® Mist	64	1.38 *(1.74)*	0.0020	1.18 *(1.70)*	0.027
Placebo	61	2.46 *(2.06)*	--	1.95 *(2.12)*	--
Duration of Bronchodilator Effect ($t_{Duration}$) *(hours)*					
Epinephrine-HFA	248	1.44 *(2.08)*	0.0092	1.37 *(2.08)*	0.018
Primatene® Mist	64	1.40 *(2.08)*	0.066	1.39 *(2.09)*	0.073
Placebo	61	0.78 *(1.62)*	--	0.78 *(1.62)*	--

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Study Report), pg. 123 (Table 7.4-2)

As would be expected, results for the secondary endpoint of $AUC_{0\text{-}6hr}$ of ΔFEV1 were similar to those for the closely related primary endpoint of $AUC_{0\text{-}6hr}$ of Δ%FEV1. In addition, epinephrine-HFA had a faster time of onset, a greater peak bronchodilator effect, a faster time to peak bronchodilator effect, and longer duration of action compared to placebo, with all comparisons demonstrating statistical significance. These results were robust to various methods of missing data handling. Most of the results for the comparison between Primatene® Mist and placebo on these secondary endpoints were also significant. Overall, these results are supportive of the findings for the primary endpoint.

6.1.6 Other Endpoints

Results of additional Trial C efficacy analyses requested by FDA, including serial FEV1 (from baseline to 360 minutes post-dose) at the start and end of treatment, as well as $AUC_{0\text{-}6hr}$ of FEV1, F_{max} of FEV1, and T_{max} of FEV1, are described in Section 6.1.4.

6.1.7 Subpopulations

The application includes an analysis of efficacy results for subpopulations, based on gender and region. It should be noted that these analyses were limited by the small sample sizes, particularly in the comparator arms. Results for the primary endpoint of $AUC_{0\text{-}6hr}$ of Δ%FEV1 at Week 12 were significant for both males and females (data not shown). The regional subgroup analysis is not reviewed, as all Trial C sites were in the United States.

The FDA's statistical review conducted subgroup efficacy analysis based on age, sex, race, and asthma severity, the results of which are provided in Table 20, Table 21, Table 22, and Table 23 , respectively. While these analyses are limited in many instances by the small sample size of various subpopulations, in general the results are consistent with those observed for the overall ITT population.

Age

Table 20. Age Subgroup Analysis for the Primary Endpoint, AUC0-6hr of Δ%FEV1 (%xhr), at Week 12, Trial C, ITT Population (Model C)

Placebo Mean (SD)	Epinephrine-HFA Mean (SD)	Primatene® Mist Mean (SD)	Mean Difference Epinephrine-HFA - Placebo (95% CI)
Adolescents (12 to <18 years)			
N=4	N=18	N=3	
7.24 (24.54)	58.06 (87.95)	66.98 (43.70)	50.82 (0.26, 101.4)*
Adults (≥ 18 years)			
N=57	N=230	N=61	
13.14 (57.43)	39.22 (52.86)	34.13 (45.58)	26.08 (9.43, 42.73)*

Source: FDA Statistical Review and Evaluation, Feng Zhou, M.S.
*p-value<0.05
Note: The mean, standard deviations, 95% confidence interval, and p-value are based on two-sided t-test analyses.

The age-based subgroup analysis compares the efficacy results for adults (patients 18 years of age and older) and adolescents (patients 12 to less than 18 years of age). It should be noted that the sample size for the adolescent population was small; nevertheless results for the primary endpoint were statistically significant across age groups.

Sex

Table 21. Sex Subgroup Analysis for the Primary Endpoint, AUC0-6hr of Δ%FEV1 (%xhr), at Week 12, Trial C, ITT Population (Model C)

Placebo Mean (SD)	Epinephrine-HFA Mean (SD)	Primatene® Mist Mean (SD)	Mean Difference Epinephrine-HFA - Placebo (95% CI)
Female			
N=40	**N=149**	**N=35**	
11.61 (47.01)	45.51 (64.28)	34.48 (44.00)	33.90 (15.78, 52.02)*
Male			
N=21	**N=99**	**N=29**	
14.94 (70.81)	33.18 (39.85)	37.10 (48.42)	18.25 (-14.80, 51.29)

Source: FDA Statistical Review and Evaluation, Feng Zhou, M.S.
*p-value<0.05
Note: The mean, standard deviations, 95% confidence interval, and p-value are based on two-sided t-test analyses.

While a treatment effect was observed across subgroups, results were statistically significant only for the larger subgroup (i.e., females).

Race

Table 22. Race Subgroup Analysis for the Primary Endpoint, AUC0-6hr of Δ%FEV1 (%xhr), at Week 12, Trial C, ITT Population (Model C)

Placebo Mean (SD)	Epinephrine-HFA Mean (SD)	Primatene® Mist Mean (SD)	Mean Difference Epinephrine-HFA - Placebo (95% CI)
Caucasian			
N=40	**177**	**N=49**	
11.08 (59.79)	41.50 (56.53)	31.92 (37.44)	30.42 (9.65, 51.18)*
African American			
N=14	**N=39**	**N=9**	
20.86 (52.79)	46.24 (53.13)	39.52 (74.03)	25.39 (-8.69, 59.46)
Hispanic/Latino			
N=4	**N=23**	**N=5**	
-4.76 (44.50)	31.67 (65.33)	64.04 (62.31)	36.44 (-28.63, 101.5)
Other			
N=3	**N=9**	**N=1**	
20.64 (35.96)	21.06 (29.16)	42.51 (--)	0.42 (-73.43, 74.27)

Source: FDA Statistical Review and Evaluation, Feng Zhou, M.S.
*p-value<0.05
Note: The mean, standard deviations, 95% confidence interval, and p-value are based on two-sided t-test analyses.

While a treatment effect was observed across all subgroups except for "Other", results were statistically significant only for the largest subgroup (i.e., Caucasians).

Asthma Severity

Table 23. Asthma Severity Subgroup Analysis for the Primary Endpoint, AUC0-6hr of Δ%FEV1 (%xhr), at Week 12, Trial C, ITT Population (Model C)

Placebo Mean (SD)	Epinephrine-HFA Mean (SD)	Primatene® Mist Mean (SD)	Mean Difference Epinephrine-HFA - Placebo (95% CI)
FEV1 %predicted < 80%			
N=52	N=213	N=52	
10.58 (53.53)	39.88 (57.52)	29.06 (41.47)	29.31 (12.59, 46.03)*
FEV1 %predicted ≥ 80%			
N=9	N=35	N=12	
25.35 (69.64)	44.90 (46.88)	64.33 (53.7)	19.55 (-35.15, 74.24)

Source: FDA Statistical Review and Evaluation, Feng Zhou, M.S.
*p-value<0.05
Note: The mean, standard deviations, 95% confidence interval, and p-value are based on two-sided t-test analyses.

While a treatment effect was observed across subgroups, results were statistically significant only for the larger subgroup (i.e., FEV1 %predicted <80%).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The epinephrine-HFA phase 3 trials evaluated only the dose currently proposed for approval, 125 mcg/inh. Data to support the selection of dose carried into the phase 3 program are reviewed in Section 4.4.2.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The primary evidence for persistence of efficacy up to 3 months comes from the 12-week results from Trial C, which are discussed in Sections 6.1.4 and 6.1.5.

6.1.10 Additional Efficacy Issues/Analyses

Since the intended use of the proposed product is as a bronchodilator in asthma, rescue medication use by patients in the clinical trials is of interest. Patients in Trials C and C2 were provided albuterol HFA MDI for use as a rescue medication, and a summary of this use is provided in Table 24.

Table 24. Rescue Medication Use, Trials C and C2

	Trial C			Trial C2		
	Placebo N=58	Epinephrine-HFA N=245	Primatene® Mist N=63	Placebo N=36	Epinephrine-HFA N=132	Primatene® Mist N=34
Patients using						

rescue medication, n (%)	51 (88)	189 (77)	53 (84)	31 (86)	111 (84)	32 (94)
Days with rescue medication use						
Mean	27.3	13.7	14.3	53.8	33.6	17.5
Min-Max	0-89	0-85	0-81	0-175	0-176	0-82
Number of inhalations per day of use						
Mean	1.12	0.94	0.98	1.01	0.61	0.37
Min-Max	0-2.32	0-3.50	0-2.26	0-6.71	0-5.46	0-2.05
Total daily rescue medication dose per day of use, mcg/day/patient						
Mean	129.5	60.3	51.7	91.3	54.5	33.5
Min-Max	0-722	0-718	0-514	0-604	0-491	0-185
Total rescue medication inhalations over trial duration, inhalations/patient						
Mean	112.8	49.6	42.8	182.8	108	46.6
Min-Max	0-642	0-678	0-480	0-1228	0-966	0-267
Total rescue medication dose over trial duration, mg/patient						
Mean	10.1	4.5	3.9	16.5	9.7	4.2
Min-Max	0-57.8	0-61.0	0-43.2	0-111	0-86.9	0-24.0

Source: Applicant's NDA 205-920 Submission dated December 20, 2013, Section 1.2 (Cover Letters), pg. 5 (Table C-a)

In Trial C, the percentage of patients using rescue medication was higher for patients on placebo (88%) compared to those receiving epinephrine-HFA (77%). Over the course of the trial patients on placebo received a total dose of albuterol HFA MDI that was approximately two-fold compared to patients on epinephrine-HFA (10.1 mg vs. 4.5 mg). In Trial C2, while the overall percentage of patients using rescue medication was similar between placebo and epinephrine-HFA (86% and 84%, respectively), the total dose received over the course of the trial was again higher for patients on placebo compared to those on epinephrine-HFA (16.5 mg vs. 9.7 mg). These data provide additional support for epinephrine-HFA's efficacy as a bronchodilator.

7 Review of Safety

Safety Summary

The premarket safety database for the proposed product consists of a 3-month phase 3 trial conducted in adults and adolescents 12 years of age and older (Trial C), combined with a 12-week extension (Trial C2). Patients enrolled in the extension were permitted to have up to a 135-day interruption in trial participation. Additional safety data is provided by a 4-week trial in pediatric patients ages 4 to 11 years.

Safety assessments conducted in the clinical development program include adverse event monitoring, clinical laboratory testing, vital signs, and 12-lead electrocardiograms (ECG). This battery of assessments is considered appropriate for the evaluation of the proposed product.

There were no deaths in the clinical development program, and only three serious adverse events (SAE). There was a low number of events leading to discontinuation, and the percentage of patients with any adverse event (AE) leading to discontinuation is balanced between the epinephrine-HFA and placebo treatment arms.

The clinical development program prospectively identified adverse events of special interest (AESI), based on the known clinical and pharmacological effects of epinephrine. Given the increase in systemic exposure documented for epinephrine-HFA compared to Primatene® Mist, particular attention was paid to systemic effects including cardiovascular effects. Adverse events designated as AESIs were tremor, chest discomfort, chest pain, tachycardia, heart rate increase, and QTc prolongation. Tremor was the most commonly reported AE for patients treated with epinephrine HFA in Trials C and C2 combined, and a notable imbalance between the proposed product and placebo is observed (10% vs. 2%, respectively); this result is expected. Chest discomfort and chest pain were more common for the epinephrine-HFA treatment arm compared to placebo, but the low number and benign nature of the observed events are reassuring. The observed mean changes in vital signs in Trial C and C2 were either balanced across treatment groups or not likely to be of clinical relevance, as were observed changes in QTc on electrocardiograms. Premature ventricular contractions (PVCs) were more common for epinephrine-HFA compared to placebo in Trial C, although the overall number of events was low. No arrhythmias were reported for either Trial C or C2. A consult review obtained from the Division of Cardiorenal Product concludes that while the total exposure in the clinical development program would allow only for the identification of catastrophic cardiovascular events, reassurance is provided by the totality of the data, which includes the absence of cardiac events in the clinical development program, projections of minimal consequences of the immediate effects of epinephrine-HFA upon vital signs, and the benign postmarketing experience with Primatene® Mist.

The safety data from the pediatric trial in children ages 4 to 11 years (Trial D) were generally unremarkable. Some imbalances in vital signs and QTc are noted, and may warrant further exploration, as the sample size in Trial D was small. A second pediatric efficacy, Trial D2, is currently underway.

In conclusion, the safety database and extent of exposure were adequate to permit review. While epinephrine's known pharmacodynamic properties include effects on the heart, the safety profile observed in the proposed product's clinical development program was generally reassuring.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

CLINICAL TRIALS USED TO EVALUATE SAFETY
The review of safety focuses on the phase 3 trials, and in particular, on the data provided by Trial C and its extension, Trial C2.

The protocols for the Phase 3 trials are discussed in detail in Section 5.3. Safety evaluations performed in these included: vital signs, 12-lead ECGs, serum potassium and glucose, additional clinical laboratory assessments, and adverse event monitoring, which were conducting according to the schedules provided in Table 8, Table 9, and Table 10.

7.1.2 Categorization of Adverse Events

The following definitions were employed by the Applicant to describe adverse events reported for the epinephrine clinical development program:

Table 25. Applicant's Definitions of Adverse Events

Category	Abbreviation	Definition	Comments
Adverse Event	AE	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.	
Serious Adverse Event	SAE	An AE that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or other important medical event that may jeopardize the patient and	Consistent 21 CFR § 312.32(a)

		may require medical or surgical intervention to prevent one of the outcomes listed.	

Source: Applicant's NDA 205-920 Submission July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Protocol or Amendment), pg. 58, 60; Section 5.3.5.1 (API-E004-CL-C2, Protocol or Amendment), pg. 31-33

Adverse events in the epinephrine clinical program were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This review of safety focuses on the phase 3 trials, and in particular, on the data provided by Trial C and its extension, Trial C2. As described below in Section 7.2.1, the protocol for Trial C2 allowed for up to a 135-day interruption in trial participation. Taking this potential interruption of treatment into consideration, safety data is presented for Trials C and C2 combined where appropriate (e.g., adverse events) and separately when the latter would be more informative (e.g., changes in vital signs). Safety data for the pediatric population ages 4 to 11 years from Trial D is reviewed separately in Section 7.6.3, and relevant safety findings from the dose-ranging trials are discussed in Section 4.4.2.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A summary of the extent of exposure provided by phase 3 trials evaluating epinephrine-HFA in adults and adolescents (Trials C and C2) is provided in Table 26. Trial C2 was a 12-week extension of Trial C, and together the two trials are intended to provide long-term safety data (i.e., 6-month data). It should be noted, however, that the protocol for Trial C2 allowed for up to a 135-day interruption in trial participation (i.e., patients eligible for enrollment in Trial C2 could have completed Trial C up to 135 days prior). The exposure data provided in Table 26 is cumulative for patients across both Trials C and C2; additional context is provided in Table 27, which summarizes the interruption in treatment between the two trials.

Table 26. Summary of Exposure, Trials C and C2 combined

	Placebo N=61	Epinephrine-HFA N=248	Primatene® Mist N=64

Exposure, days			
Mean (SD)	142 ± 59	131 ± 58	102 ± 31
Median	181	178	108
Min, Max	1, 244	1, 199	1, 142
Range, n (%)			
≥ 1 day	61 (100)	248 (100)	64 (100)
≥ 7 days	59 (97)	246 (99)	62 (97)
≥ 28 days	58 (95)	232 (94)	61 (95)
≥ 56 days	56 (92)	220 (89)	60 (94)
≥ 84 days	48 (79)	204 (82)	53 (83)
≥ 112 days	38 (62)	134 (54)	27 (42)
≥ 140 days	38 (62)	132 (53)	4 (6)
≥ 168 days	37 (61)	127 (51)	0 (0)

Source: Applicant's NDA 205-920 Submission dated December 20, 2013, Section 1.2 (Cover Letters), pg. 2 (Table A)
Note: N=Number of patients in the Treated Population

Table 27. Interruption in Treatment Between Trial C and Trial C2

	Placebo N=61	Epinephrine-HFA N=248	Primatene® Mist N=64
Interruption, days			
Mean (SD)	78 ± 29	75 ± 27	81 ± 25
Median	75	77	88
Min, Max	26, 129	13, 141	15, 131

Source: Applicant's NDA 205-920 Submission dated December 20, 2013, Section 1.2 (Cover Letters), pg. 3 (Table B)
Note: N=Number of patients in the Treated Population

Across Trials C and C2 combined, 204 patients were treated with epinephrine-HFA for at least 84 days (12 weeks), and 127 patients were treated for at least 168 days (24 weeks). The mean duration of treatment interruption was 75-81 days across treatment arms. While the overall number of patients treated for 6 months or longer is adequate, reliance on data from Trials C and C2 as evidence for "long-term" safety must take into account this degree of interrupted treatment.

The disposition of patients participating Trials C and C2 combined is provided in Table 28.

Table 28. Subject Disposition, Trials C and C2 combined

	Placebo N=61	Epinephrine-HFA N=248	Primatene® Mist N=64
Patients who discontinued, n (%)	6 (10)	40 (16)	44 (69)
Reasons for Discontinuation			

Personal/withdrawal of consent	0	11 (4)	3 (5)
Lost to follow-up	2 (3)	3 (1)	1 (2)
Protocol violation	0	7 (3)	2 (3)
Adverse event	4 (7)	19 (8)	3 (5)
Mandated Sunset of Primatene® Mist	NA	NA	35 (55)

Source: Applicant's NDA 205-920 Submission dated December 20, 2013, Section 1.2 (Cover Letters), pg. 15 (Table D)
Note: N=Number of patients in the Treated Population
Key: NA=Not applicable

The percentage of patients who were discontinued from Trials C and C2 was slightly higher for the epinephrine-HFA group compared to placebo (16% and 10%, respectively), but withdrawals due to adverse events were comparable between these two groups. The percentage of patients who were discontinued was much higher for the Primatene® Mist treatment group, reflecting the mandated sunset of this product.

Demographic and asthma disease characteristics of patients in Trial C are described in Section 6.1.2 (Table 11 and Table 12, respectively).

7.2.2 Explorations for Dose Response

The epinephrine-HFA phase 3 trials evaluated only the maximum dose currently proposed for approval, 125 mcg/inh x 2 inhalations. Data to support the selection of dose carried into the phase 3 program are reviewed in Section 4.4.2.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was conducted in support of this application.

7.2.4 Routine Clinical Testing

The routine clinical testing in the phase 3 trials included: serum potassium and glucose, additional clinical laboratory assessments, and 12-lead ECGs. The routine clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The clinical development program did not include a specific evaluation for drug-drug interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The clinical development program prospectively identified adverse events of special interest (AESI), based on the known clinical and pharmacological effects of epinephrine. Adverse events designated as AESIs were tremor, chest discomfort, chest pain, tachycardia and heart rate increase, and QTc prolongation. Results of these analyses are provided in Section 7.3.5.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported for the epinephrine-HFA clinical development program.

7.3.2 Nonfatal Serious Adverse Events

There were a total of three nonfatal serious adverse events (SAEs) reported for the epinephrine-HFA clinical development program: two SAEs were reported for epinephrine-HFA (both in Trial C2), and one SAE was reported for Primatene® Mist (in Trial C). A brief summary of these three SAEs is provided below.

Epinephrine-HFA
Patient ID: (b) (6)
This SAE was an event of "left breast cancer" reported for a 59 year old female. Approximately 2 months after starting treatment with epinephrine-HFA the patient reported she was diagnosed with cancer of the left breast. The patient completed the trial. The Investigator assessed this event to be unrelated to study drug.

Patient ID: (b) (6)
This SAE was an event of "pregnancy" reported for a 33 year old female. The Investigator assessed this event to be unrelated to study drug.

Primatene® Mist
Patient ID: (b) (6)
This SAE was an event of "acute bronchitis" reported for a 58 year-old male with a history of asthma, pneumonia, and diabetes. Approximately 3 weeks after staring treatment with Primatene® Mist the patient developed "acute bronchitis" two hours after dosing. He was admitted to the Emergency Department where evaluation included a chest radiograph and computed tomography scan. Treatments administered included moxifloxacin and albuterol-ipratropium. He was discharged the next day. The event

resolved in three days, and the patient completed the trial. The Investigator assessed the event as having an unknown relationship to study drug.

The number of non-fatal SAEs in the clinical development program was low. The two SAEs reported in the epinephrine-HFA arm appear to be unrelated to treatment.

7.3.3 Dropouts and/or Discontinuations

Adverse events leading to discontinuation with an incidence greater than or equal to two (in any treatment arm) in Trials C and C2 combined are presented in Table 29.

Table 29. Adverse Events Leading to Discontinuation Reported with an Incidence ≥ 2 in any Treatment Arm, by SOC and PT, Trials C and C2 combined

	Placebo N=61	Epinephrine-HFA N=248	Primatene® Mist N=64
	n (%)	n (%)	n (%)
AEs leading to discontinuation	**6 (10)**	**26 (11)**	**3 (5)**
Respiratory System			
Any event	3 (5)	10 (4)	2 (3)
Asthma	1 (2)	5 (2)	2 (3)
Nervous System			
Any event	2 (3)	6 (2)	0
Tremor	1 (2)	3 (1)	0
Digestive System			
Any event	0	3 (1)	0
Throat Irritation	0	2 (1)	0

Source: Applicant's NDA 205-920 Submission January 24, 2014, Cover Letter, pg. 2 (Table EU)
Note: N=Number of patients in the Treated Population; n=number of occurrences of AE; %=n/N

The overall percentage of AEs leading to discontinuation is balanced between the epinephrine-HFA and placebo treatment arms (10-11%), and lower for the Primatene® Mist treatment arm (5%). Most notable are the low number of events leading to discontinuation; there are only a few preferred terms reported for 2 or more patients in any treatment arm. Tremor is reviewed as an adverse event of special interest (AESI) in Section 7.3.5 of this review.

7.3.4 Significant Adverse Events

Adverse events leading to dropout are discussed in Section 7.3.3. There were no events leading to dose reduction, as dose reduction was not performed in the phase 3 trials. Adverse events of special interest are discussed in Section 7.3.5.

7.3.5 Submission Specific Primary Safety Concerns

The clinical development program prospectively identified adverse events of special interest (AESI), based on the known clinical and pharmacological effects of epinephrine. Adverse events designated as AESIs were tremor, chest discomfort, chest pain, tachycardia, heart rate increase, and QTc prolongation. The number and percentage of patients reporting these events in Trial C and C2 combined is provided in Table 30.

Table 30. Adverse Events of Special Interest, Trial C and C2 combined

	Placebo N=61	Epinephrine-HFA N=248	Primatene® Mist N=64
Tremor	1 (2)	24 (10)	1 (2)
Chest discomfort	1 (2)	9 (4)	1 (2)
Chest pain	0	3 (1)	0
Tachycardia	0	1 (0.4)	0
Heart rate increase	0	1 (0.4)	0
QTc prolongation	0	0	0

Source: Applicant's NDA 205-920 Submission dated December 20, 2013, Section 1.2 (Cover Letters), pg. 10-12 (Table ISS-23U)
Note: N=Number of patients in the Treated Population

Tremor

Tremor was the most commonly reported AE for patients treated with epinephrine-HFA in Trials C and C2 combined, and a notable imbalance between the proposed product and placebo is observed (10% vs. 2%, respectively); this is to be expected. While the low incidence of tremor in the Primatene® Mist comparator arm (2%) is somewhat surprising, one possible explanation for the imbalance between the two epinephrine arms is the difference in C_{max}, which is higher for epinephrine-HFA. While tremor was commonly reported, none of the events was classified as an SAE, and only one was classified as a severe AE. While the event classified as severe and resulted in the patient's discontinuation, the event was noted to resolve without residual effect. A total of three events of tremor resulted in patients' discontinuation from Trials C and C2 (see Table 29).

Chest Discomfort and Chest Pain

Chest discomfort was among the most commonly reported AEs for patients treated with epinephrine-HFA, and an imbalance is noted for the proposed product compared to both placebo and Primatene® Mist (4% for epinephrine-HFA compared to 2% for placebo and 2% for Primatene® Mist). Of the 9 events reported for the epinephrine-HFA arm, three events occurred in a single patient and two events occurred in another patient. None of the events was classified as an SAE, and all were noted to resolve without residual effect.

Chest pain was less commonly reported than chest discomfort. The overall numbers of adverse events of chest pain were low for the epinephrine-HFA group (n=3), but an imbalance is nonetheless noted, as there were zero events in the other two treatment arms. None of the three events were classified as SAEs, and all were noted to resolve without residual effect.

Tachycardia, Heart Rate Increase, and QTc Prolongation

There were very few AESIs of tachycardia and heart rate increase, and no AEs of QTc prolongation. No patterns are discernible given the low number of events. An analysis of vital sign data and electrocardiogram data is provided in Sections 7.4.3 and 7.4.4, respectively, of this review.

SUMMARY OF CARDIOVASCULAR SAFETY PROFILE

As noted above, the Applicant prospectively identified adverse events of special interest based on epinephrine's known clinical and pharmacological effects. These included events related to cardiovascular safety, including chest discomfort, chest pain, tachycardia, heart rate increase, and QTc prolongation. Overall, the low number and benign nature of the observed events are reassuring.

In addition to the analysis of cardiovascular AESIs, the assessment of cardiovascular safety for epinephrine-HFA also includes an examination of vital signs (heart rate, systolic and diastolic blood pressure) and ECG parameters in Trials C and C2, which are described in Sections 7.4.3 and 7.4.4, respectively, of this review. The effect of epinephrine-HFA on vital signs was also evaluated in the high-dose trials conducted in healthy volunteers (Trials B, B2, and B3). The Division of Cardiovascular and Renal Products (DCRP) reviewed data from the epinephrine-HFA clinical development program, and concluded that, "while we note some limitations to the clinical trial designs and conduct, we judge them adequate to provide some reassurance regarding the cardiac safety of E004 [epinephrine-HFA] at the proposed to-be-marketed dose" (DCRP consult review, December 5, 2013). More specifically, the DCRP consult review notes the following:

- The total exposure in the clinical development program would allow only for the identification of catastrophic cardiovascular events; however, reassurance is provided by the totality of the data, which includes the absence of cardiac events in the clinical development program, projections of minimal consequences of the immediate effects of epinephrine-HFA upon vital signs, and the benign postmarketing experience with Primatene® Mist
- Changes in vital signs with epinephrine-HFA at the proposed to-be-marketed dose appear modest; however, this evaluation is limited by the noisy nature of the data, which could obscure larger vital sign changes in some patients
- The high-dose trials were generally limited by the lack of vital sign data in the early period after dosing (to coincide with T_{max})

- Results from the most relevant high-dose trial in healthy volunteers (Trial B) suggest that increases in systolic blood pressure and heart rate with epinephrine-HFA can be substantial in some patients; this would be relevant to overdose or abuse situations. Conversely, the data from Trial B confirm that the changes in blood pressure and heart rate expected with the proposed to-be-marketed dose are modest
- The postmarketing reports for Primatene® Mist identified through an analysis of Adverse Event Reporting System (AERS) data were not concerning from a cardiovascular safety perspective
- While limitations in trial design and conduct are noted, overall the data is adequate for providing some reassurance about the cardiac safety of epinephrine-HFA at the proposed to-be-marketed dose. Given the relatively unconcerning findings in the submitted clinical data, a large, cardiovascular outcome study is not recommended

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events reported for 3% or more of patients (in any treatment group) in Trials C and C2 combined are provided in Table 31.

Table 31. Common Adverse Events Reported for ≥ 3% Patients in the Epinephrine-HFA arm and greater than placebo, by PT, Trials C and C2 combined

	Placebo N=61	Epinephrine-HFA N=248	Primatene® Mist N=64
All AEs	63 (103)	352 (142)	52 (81)
Tremor	1 (2)	24 (10)	1 (2)
Throat irritation	0	13 (5)	1 (2)
Cough	0	11 (4)	1 (2)
Sinusitis	2 (3)	9 (4)	0
Chest discomfort	1 (2)	9 (4)	1 (2)
Feeling jittery	0	8 (3)	0
Bronchitis	1 (2)	7 (3)	1 (2)
Dizziness	1 (2)	7 (3)	0

Source: Applicant's NDA 205-920 Submission dated December 20, 2013, Section 1.2 (Cover Letters), pg. 7 (table ISS-22U), pg. 10-12 (Table ISS-23U)
Note: N=Number of patients in the Treated Population; n=number of occurrences of AE; %=n/N

In Trials C and C2 combined, an imbalance in the overall percentage of AEs is noted between epinephrine-HFA and the other treatment arms. As described in Section 7.3.5,

tremor was the most commonly reported AE for epinephrine-HFA, and a notable imbalance favoring placebo was observed. Other common AEs reported in at least 3% of patients in the epinephrine-HFA arm and more often than for placebo were throat irritation, cough, sinusitis, chest discomfort, feeling jittery, bronchitis, and dizziness. With the exception of throat irritation, cough, and feeling jittery, the magnitude of imbalance between the epinephrine-HFA and placebo arms for these AEs was small.

7.4.2 Laboratory Findings

Chemistry

Change in mean values for chemistry parameters over the course of Trial C (from Screening to Visit 5), and over the course of Trial C2 (from Screening to Visit 8) are provided in Table 32 and Table 33.

Table 32. Change in Mean Values for Chemistry Parameters, Trial C

	Placebo			Epinephrine-HFA			Primatene® Mist		
	SCR *Mean ± SD*	EOS *Mean ± SD*	Δ	EOS *Mean ± SD*	SCR *Mean ± SD*	Δ	EOS *Mean ± SD*	SCR *Mean ± SD*	Δ
Sodium	139.4 ±2.3	139.7 ±2.5	0.3	139.8 ±2.0	139.5 ±2.1	-0.3	140.0 ±2.1	140.1 ±2.0	0.1
Potassium	4.3 ±0.4	4.3 ±0.4	0.0	4.3 ±0.4	4.3 ±0.4	0.0	4.4 ±0.4	4.4 ±0.4	0.0
Chloride	102.8 ±2.3	103.4 ±2.4	0.6	103.2 ±2.1	103.1 ±2.3	-0.1	103.0 ±2.4	103.7 ±2.5	0.7
Bicarbonate	25.7 ±2.5	26.0 ±2.5	0.3	25.2 ±2.6	25.5 ±2.8	0.3	25.6 ±2.3	25.6 ±2.5	0.0
Urea Nitrogen	13.3 ±3.4	12.6 ±3.5	-0.7	14.0 ±4.2	13.6 ±4.0	-0.4	13.9 ±4.1	13.7 ±3.3	-0.2
Creatinine	0.8 ±0.2	0.8 ±0.2	0	0.8 ±0.2	0.8 ±0.2	0	0.8 ±0.2	0.8 ±0.2	0
Glucose	94.2 ±18.3	91.6 ±21.1	-2.6	95.9 ±19.5	92.7 ±25.0	-3.2	97.3 ±19.8	91.1 ±11.1	-6.2
Calcium	9.7 ±0.3	9.6 ±0.4	-0.1	9.7 ±0.4	9.7 ±0.4	0	9.8 ±0.4	9.6 ±0.4	-0.2
Total Protein	7.1 ±0.4	7.0 ±0.4	-0.1	7.1 ±0.4	7.0 ±0.4	-0.1	7.0 ±0.4	7.0 ±0.3	0
Albumin	4.3 ±0.2	4.3 ±0.3	0	4.4 ±0.3	4.4 ±0.3	0	4.4 ±0.3	4.4 ±0.2	0
ALT	19.7 ±10.1	20.5 ±11.6	0.8	22.4 ±14.8	22.9 ±14.9	0.5	20.7 ±8.4	19.7 ±9.0	-1.0
AST	20.9	22.2	1.3	21.8	22.6	0.8	21.1	20.7	-0.4

	±6.7	±7.8		±11.2	±18.7		±6.1	±6.5	
ALP	80.1 ±50.0	80.2 ±53.0	0.1	78.8 ±49.4	77.2 ±51.9	-1.6	79.5 ±46.0	79.4 ±57.2	-0.1

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Study Report), pg. 185 (Table 8-13)
Key: EOS=end of study (i.e., Visit 5); SCR=screening; Δ=change

Table 33. Change in Mean Values for Chemistry Parameters, Trial C2

	Placebo			Epinephrine-HFA			Primatene® Mist		
	SCR *Mean ± SD*	**EOS** *Mean ± SD*	**Δ**	**EOS** *Mean ± SD*	**SCR** *Mean ± SD*	**Δ**	**EOS** *Mean ± SD*	**SCR** *Mean ± SD*	**Δ**
Sodium	140.0 ±2.8	139.7 ±2.2	-0.3	139.7 ±2.1	139.8 ±2.4	0.1	140.3 ±1.7	140.4 ±1.6	0.1
Potassium	4.2 ±0.4	4.3 ±0.4	0.1	4.3 ±0.4	4.3 ±0.4	0.0	4.3 ±0.3	4.2 ±0.3	-0.1
Chloride	102.9 ±2.5	103.5 ±2.1	0.6	102.5 ±2.3	103.3 ±2.1	0.8	102.9 ±2.1	103.9 ±2.4	1.0
Bicarbonate	25.7 ±2.6	24.6 ±2.2	-1.1	25.9 ±2.4	24.9 ±2.2	-1.0	25.7 ±2.6	25.4 ±2.3	-0.3
Urea Nitrogen	13.4 ±4.8	13.2 ±3.9	-0.2	14.5 ±4.4	14.0 ±4.1	-0.5	14.4 ±4.0	14.4 ±3.0	0
Creatinine	0.8 ±0.2	0.8 ±0.2	0	0.8 ±0.2	0.8 ±0.2	0	0.8 ±0.2	0.9 ±0.2	0.1
Glucose	90.8 ±10.5	91.1 ±9.7	0.3	90.4 ±21.7	92.9 ±19.7	2.5	90.3 ±14.0	90.9 ±10.8	0.6
Calcium	9.6 ±0.4	9.4 ±0.3	-0.2	9.6 ±0.4	9.4 ±0.4	-0.2	9.6 ±0.3	9.4 ±0.3	-0.2
Total Protein	7.0 ±0.3	6.9 ±0.4	-0.1	7.0 ±0.4	6.9 ±0.4	-0.1	7.0 ±0.4	6.9 ±0.3	-0.1
Albumin	4.3 ±0.2	4.2 ±0.2	-0.1	4.3 ±0.3	4.3 ±0.3	0	4.3 ±0.2	4.3 ±0.2	0
ALT	24.5 ±17.6	23.3 ±15.5	-1.2	21.4 ±11.9	21.6 ±10.5	0.1	23.5 ±17.9	18.8 ±7.4	-4.7
AST	27.7 ±32.9	22.2 ±7.3	-5.5	21.5 ±7.0	20.5 ±6.0	-1.0	22.4 ±9.6	19.4 ±5.8	-3.0
ALP	77.4 ±27.8	75.6 ±26.0	-1.8	77.2 ±54.9	77.3 ±53.1	0.1	81.3 ±54.0	67.1 ±20.6	-14.2

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C2, Study Report), pg. 314 (Table 8-13)
Key: EOS=end of study (i.e., Visit 8); SCR=screening; Δ=change

In general, baseline mean values and the change in mean values from screening to the end of study were balanced across treatment arms in both Trial C and Trial C2. One exception is the change in glucose in Trial C2: a greater increase is observed for

epinephrine-HFA compared to placebo, which is expected. A similar pattern is not observed in Trial C.

Given the known pharmacologic effects of epinephrine, careful attention to changes in glucose and potassium parameters is warranted. Adrenergic drugs may cause increases in glucose (hyperglycemia) and decreases in potassium (hypokalemia). To further explore the impact of epinephrine-HFA on these laboratory parameters, shifts in glucose and potassium values observed in Trial C and C2 were examined. The percentage of patients experiencing a shift in these parameters to above or below normal is provided in Table 34 for Trial C and Table 35 for Trial C2.

Table 34. Shift Table of Glucose and Potassium Parameters, Trial C

	Placebo N=61	Epinephrine-HFA N=248	Primatene® Mist N=64
Glucose			
N1	56	215	55
To above normal range, n (%)	3 (5)	12 (6)	1 (2)
To below normal range, n (%)	2 (4)	3 (1)	1 (2)
Potassium			
N1	56	215	55
To above normal range, n (%)	5 (9)	18 (8)	7 (13)
To below normal range, n (%)	3 (5)	3 (1)	2 (4)

Source: Applicant's NDA 205-920 Submission dated December 20, 2013, Section 1.2 (Cover Letters), pg. 17 (Table F)
Note: N=Number of patients in the Treated Population; N1=number of patients with available data
Note: Sampling time is at End of Study

Table 35. Shift Table of Glucose and Potassium Parameters, Trial C2

	Placebo N=38	Epinephrine-HFA N=134	Primatene® Mist N=35
Glucose			
N1	38	131	17
To above normal range, n (%)	0	5 (4)	0
To below normal range, n (%)	0	0	0
Potassium			
N1	38	131	17
To above normal range, n (%)	1 (3)	6 (5)	0
To below normal range, n (%)	0	3 (2)	0

Source: Applicant's NDA 205-920 Submission dated December 20, 2013, Section 1.2 (Cover Letters), pg. 18 (Table G)
Note: N=Number of patients in the Treated Population; N1=number of patients with available data
Note: Sampling time is at End of Study

With regard to shifts in glucose, a small imbalance between the epinephrine-HFA and placebo in the percentage of patients with a shift to above normal range is noted for Trial C2, but not Trial C. With regard to the potassium parameter, there are no

imbalances in the percentage of patients with a shift to below normal range in either Trial C and C2; an imbalance between Primatene® Mist and the other arms in Trial C is observed for the percentage of patients with a shift to below normal range, but this is opposite the direction expected and unlikely to be clinically relevant.

Overall, the analysis of the chemistry laboratory data from Trials C and C2 is reassuring.

Hematology

Change in mean values for hematology parameters over the course of Trial C (from Screening to Visit 5), and over the course of Trial C2 (from Screening to Visit 8) are provided in Table 36 and Table 37.

Table 36. Change in Mean Values for Hematology Parameters, Trial C

	Placebo			Epinephrine-HFA			Primatene® Mist		
	SCR *Mean ± SD*	EOS *Mean ± SD*	Δ	EOS *Mean ± SD*	SCR *Mean ± SD*	Δ	EOS *Mean ± SD*	SCR *Mean ± SD*	Δ
WBC	6.4 ±1.8	6.2 ±1.6	-0.2	6.5 ±1.7	6.4 ±1.7	-0.1	6.3 ±1.7	6.5 ±1.8	0.2
Absolute Lymphocytes	2.0 ±0.6	1.9 ±0.6	-0.1	2.0 ±0.6	1.9 ±0.5	-0.1	2.0 ±0.5	2.0 ±0.6	0
Absolute Neutrophils	3.7 ±1.4	3.7 ±1.2	0	3.8 ±0.3	3.9 ±0.4	0.1	3.6 ±1.5	3.9 ±1.5	0.3
Absolute Monocytes	0.4 ±0.1	0.3 ±0.1	-0.1	0.4 ±0.1	0.4 ±0.1	0	0.4 ±0.1	0.4 ±0.1	0
Absolute Basophils	0.0 ±0.0	0.0 ±0.0	0	0.0 ±0.0	0.0 ±0.0	0	0.0 ±0.0	0.0 ±0.0	0
Absolute Eosinophils	0.2 ±0.2	0.2 ±0.2	0	0.3 ±0.2	0.2 ±0.2	-0.1	0.3 ±0.2	0.2 ±0.1	-0.1
Hemoglobin	13.4 ±1.4	13.3 ±1.7	-0.1	14.1 ±1.3	14.0 ±1.3	-0.1	14.0 ±1.2	14.0 ±1.3	0

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Study Report), pg. 464 (Table 8-13)
Key: EOS=end of study (i.e., Visit 5); SCR=screening; Δ=change

Table 37. Change in Mean Values for Hematology Parameters, Trial C2

	Placebo			Epinephrine-HFA			Primatene® Mist		
	SCR *Mean ± SD*	EOS *Mean ± SD*	Δ	EOS *Mean ± SD*	SCR *Mean ± SD*	Δ	EOS *Mean ± SD*	SCR *Mean ± SD*	Δ
WBC	6.8	6.3	-0.5	6.4	6.4	0	6.3	6.4	0.1

	±2.2	±2.3		±2.1	±2.0		±1.6	±1.6	
Absolute Lymphocytes	2.0 ±0.7	2.0 ±0.6	0	1.8 ±0.5	1.8 ±0.6	0	1.9 ±0.5	1.9 ±0.5	0
Absolute Neutrophils	4.2 ±1.9	3.7 ±1.8	-0.5	3.9 ±1.7	3.9 ±1.7	0	3.7 ±1.4	3.9 ±1.2	0.2
Absolute Monocytes	0.3 ±0.1	0.3 ±0.1	0	0.4 ±0.1	0.4 ±0.1	0	0.4 ±0.1	0.4 ±0.1	0
Absolute Basophils	0.0 ±0.0	0.0 ±0.0	0	0.0 ±0.0	0.0 ±0.0	0	0.0 ±0.0	0.0 ±0.0	0
Absolute Eosinophils	0.2 ±0.1	0.3 ±0.2	0.1	0.2 ±0.1	0.2 ±0.2	0	0.3 ±0.2	0.3 ±0.2	0
Hemoglobin	13.4 ±1.4	13.4 ±1.5	0	14.0 ±1.4	14.0 ±1.4	0	13.8 ±1.1	13.8 ±1.1	0

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C2, Study Report), pg. 314 (Table 8-13)
Key: EOS=end of study (i.e., Visit 8); SCR=screening; Δ=change

In general, baseline mean values and the change in mean values from screening to the end of study were balanced across treatment arms in both Trial C and Trial C2.

7.4.3 Vital Signs

Vital signs were evaluated over the 360 minutes after dosing at Visit 1 (Day 1), Visit 3 (Week 6), and Visit 5 (Week 12) in Trial C. Mean change in systolic blood pressure, diastolic blood pressure, and heart rate at the start and end of treatment in Trial C (i.e., Visits 1 and 5) are provided in Table 38. The observed mean changes in vital signs were either balanced across treatment groups or not likely to be of clinical relevance.

Table 38. Mean Change in Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate, Trial C

	Placebo N=61			Epinephrine-HFA N=248			Primatene® Mist N=64		
	N1	Mean	Mean Δ (Upper 95% CI)	N1	Mean	Mean Δ (Upper 95% CI)	N1	Mean	Mean Δ (Upper 95% CI)
Systolic Blood Pressure (mmHg)									
Visit 1 (Day1)									
0 min	61	117	0.0 (-)?	248	118	0.0 (-)?	63	118	0.0 (-)?
2 min	61	118	0.5 (2.6)	248	119	0.7 (1.6)	64	121	2.5 (4.5)
10 min	60	117	-0.1 (1.8)	248	118	0.4 (1.3)	64	121	2.3 (4.2)
20 min	61	117	-0.2 (1.7)	248	118	0.1 (1.1)	64	120	1.5 (3.6)
60 min	60	118	0.4 (2.5)	248	119	0.7 (1.7)	62	121	2.6 (4.6)
360 min	57	118	1.8 (3.9)	240	120	1.7 (2.7)	61	121	3.2 (4.8)
Visit 5 (Week 12)									
0 min	56	115	0.0 (-)?	215	119	0.0 (-)	55	120	0.0 (-)
2 min	56	115	0.1 (2.2)	215	120	0.6 (1.6)	55	120	-0.2 (2.0)

10 min	56	115	0.0 (1.9)	215	118	-1.1 (-0.1)	54	120	-0.1 (2.1)
20 min	56	115	-0.3 (1.8)	214	118	-0.9 (0.1)	55	119	-0.5 (1.5)
60 min	56	116	0.5 (2.7)	215	119	0.3 (1.4)	55	120	0.7 (2.6)
360 min	54	119	4.1 (6.9)	211	120	1.1 (2.3)	54	123	2.9 (5.3)
Diastolic Blood Pressure (mmHg)									
Visit 1 (Day1)									
0 min	61	74	0.0 (-)?	248	75	0.0 (-)?	63	76	0.0 (-)?
2 min	61	74	0.2 (1.7)	248	75	0.5 (1.3)	64	77	1.3 (2.7)
10 min	60	75	1.0 (2.7)	248	75	0.3 (1.1)	64	77	0.9 (2.5)
20 min	61	74	-0.1 (1.3)	248	76	0.9 (1.7)	64	76	-0.4 (1.1)
60 min	59	76	1.7 (3.3)	248	76	1.3 (2.1)	62	78	1.4 (2.8)
360 min	56	73	-0.3 (1.4)	240	74	-0.1 (0.7)	61	75	-1.4 (-0.1)
Visit 5 (Week 12)									
0 min	56	74	0.0 (-)?	215	75	0.0 (-)	55	75	0.0 (-)
2 min	56	74	-0.5 (0.9)	215	75	0.2 (1.0)	55	75	0.1 (1.9)
10 min	56	74	0.0 (1.5)	215	75	0.1 (0.9)	54	76	0.1 (1.9)
20 min	56	75	0.8 (2.2)	214	76	1.0 (1.8)	55	76	1.1 (3.0)
60 min	56	75	0.8 (2.5)	215	76	1.1 (2.0)	55	77	1.3 (3.0)
360 min	54	74	-0.2 (1.6)	211	74	-0.6 (0.3)	54	76	1.1 (2.8)
Heart Rate (bpm)									
Visit 1 (Day1)									
0 min	61	71	0.0 (-)?	248	70	0.0 (-)	63	71	0.0 (-)
2 min	61	68	-3.7 (-2.5)	248	70	0.2 (1.0)	64	70	-0.8 (0.3)
10 min	60	68	-3.0 (-1.5)	248	68	-1.8 (-1.1)	64	70	-0.7 (0.8)
20 min	61	67	-4.7 (-3.2)	248	67	-3.2 (-2.4)	64	67	-3.7 (-2.3)
60 min	60	66	-6.0 (-4.6)	248	66	-3.7 (-3.0)	62	67	-3.7 (-2.2)
360 min	57	72	1.0 (3.0)	240	70	0.8 (1.7)	61	72	1.5 (3.1)
Visit 5 (Week 12)									
0 min	56	71	0.0 (-)	215	69	0.0 (-)	55	71	0.0 (-)
2 min	56	70	-1.8 (-0.3)	215	69	-0.2 (0.7)	55	70	-0.7 (1.4)
10 min	56	70	-1.4 (0.2)	215	68	-1.6 (-0.8)	54	69	-1.7 (-0.1)
20 min	56	68	-3.9 (-2.4)	214	66	-3.2 (-2.4)	55	67	-3.3 (-1.7)
60 min	56	67	-4.0 (-2.4)	215	66	-3.7 (-2.8)	55	66	-4.3 (-2.3)
360 min	54	73	1.6 (3.6)	210	71	2.0 (3.0)	54	73	2.7 (5.1)

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Study Report), pg. 467 (Table 8.5-2), pg. 468 (Table 8.5-3)
Key: Δ=change compared to same-day baseline
Note: N=Number of patients in the Treated Population; N1=number of patients with available data

Vital signs were evaluated at screening and at a single time point at least one hour after dosing during each of the eight visits (Visits 1-8) during the 3-month treatment period in Trial C2. Change in systolic blood pressure, diastolic blood pressure, and heart rate at the screening visit and Visits 1-8 are provided in Table 39. The observed changes in vital signs were either balanced across treatment groups or not likely to be of clinical relevance.

Table 39. Change in Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate, Trial C2

	Placebo N=38	Epinephrine-HFA N=134	Primatene® Mist N=35

	Value	Δ%	Value	Δ%	Value	Δ%
Systolic Blood Pressure (mmHg)						
Screening	118±13	--	120±12	--	118±13	--
Visit 1 (Day 1)	117±12	-0.8%	118±13	-1.7%	118±13	0
Visit 2 (Week 2)	119±13	0.8%	120±13	0	119±12	0.8%
Visit 3 (Week 4)	118±11	0	120±12	0	118±10	0
Visit 4 (Week 6)	119±12	0.8%	119±12	-0.8%	120±14	1.7%
Visit 5 (Week 8)	118±11	0	120±13	0	124±16	5.1%
Visit 6 (Week 10)	117±13	-0.8%	120±13	0	*	*
Visit 7 (Week 12)	118±13	0	119±13	-0.8%	*	*
Visit 8 (Week 14)	117±15	-0.8%	119±12	-0.8%	*	*
Diastolic Blood Pressure (mmHg)						
Screening	74±10	--	76±9	--	76±10	--
Visit 1 (Day 1)	74±9	0	74±11	-2.6%	75±10	-1.3%
Visit 2 (Week 2)	74±8	0	76±9	0	75±9	-1.3%
Visit 3 (Week 4)	75±8	1.4%	75±10	-1.3%	75±10	-1.3%
Visit 4 (Week 6)	74±9	0	75±9	-1.3%	75±10	-1.3%
Visit 5 (Week 8)	74±8	0	75±9	-1.3%	75±13	-1.3%
Visit 6 (Week 10)	73±7	-1.4%	74±9	-2.6%	*	*
Visit 7 (Week 12)	73±7	-1.4%	75±8	-1.3%	*	*
Visit 8 (Week 14)	77±16	4.1%	75±9	-1.3%	*	*
Heart Rate (bpm)						
Screening	70±10	--	70±11	--	68±9	--
Visit 1 (Day 1)	72±10	2.9%	73±11	4.3%	71±10	4.4%
Visit 2 (Week 2)	74±9	5.7%	73±11	4.3%	72±11	5.9%
Visit 3 (Week 4)	73±9	4.3%	73±11	4.3%	74±10	8.8%
Visit 4 (Week 6)	70±10	0	72±11	2.9%	70±9	2.9%
Visit 5 (Week 8)	73±8	4.3%	73±10	4.3%	71±10	4.4%
Visit 6 (Week 10)	72±9	2.9%	73±10	4.3%	*	*
Visit 7 (Week 12)	72±9	2.9%	74±10	5.7%	*	*
Visit 8 (Week 14)	70±10	0	71±11	1.4%	*	*

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C2, Study Report), pg. 316 (Table 8-15)
***Data not available due to withdrawal of patients after the sunset of Primatene® Mist**
Key: Δ%=change from baseline (Screening)
Note: N=Number of patients in the Treated Population

The Applicant also provided an evaluation of the heart rate data for outliers in Trial C, i.e., patients with a change in heart rate of greater than 20 bpm. There were a total of 41 events of heart rate greater than 20 bpm; the majority (35 of the 41) events were for patients in the epinephrine-HFA arm. A little more than half of the events (23 of the 41) occurring within 60 minutes of dosing; an analysis of these events is provided in Table 40. Events were more common for the epinephrine-HFA arm at each time point.

Table 40. Changes in Heart Rate Greater than 20 bpm in the first 60 minutes after dosing, Trial C

	Placebo N=61 N1=174	Epinephrine-HFA N=248 N1=684	Primatene® Mist N=64 N1=179

	n (%)	n (%)	n (%)
2 minutes	0	12 (2)	1 (1)
10 minutes	0	4 (1)	0
20 minutes	0	4 (1)	0
60 minutes	0	2 (<1)	0

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Study Report), pg. 472 (Table 8.5-4)
Note: N=Number of patients in the Treated Population; N1=number of data points (across 3 visits); n=number of events; %=percentage of data points with event

Tachycardia and heart rate increase were prospectively identified as adverse events of interest, and are discussed in Section 7.3.5; these adverse events were uncommon in the epinephrine-HFA clinical development program.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms (ECGs) were obtained over the 60 minutes after dosing at Visit 1 (Day 1) and Visit 5 (Week 12) in Trial C. Mean change in QTc at the start and end of treatment is provided in Table 41. The observed mean changes in QTc were either balanced across treatment groups or not likely to be of clinical relevance.

Table 41. Mean Change in QTc (ms), Trial C

	Placebo N=61			Epinephrine-HFA N=248			Primatene® Mist N=64		
	N1	Mean	Mean Δ (Upper 95% CI)	N1	Mean	Mean Δ (Upper 95% CI)	N1	Mean	Mean Δ (Upper 95% CI)
Visit 1 (Day1)									
0 min	59	412	0 (-)	241	411	0 (-)	62	414	0 (-)
2 min	61	411	-0.8 (1.9)	245	412	0.4 (1.9)	64	411	-2.7 (0.6)
10 min	59	413	1.1 (4.2)	246	414	2.5 (4.0)	64	414	0.6 (3.4)
20 min	60	412	-0.4 (2.4)	246	412	1.1 (2.5)	64	415	1.5 (4.4)
60 min	59	412	-0.2 (2.8)	246	408	-3.6 (-0.7)	63	413	-1.0 (2.3)
Visit 5 (Week 12)									
0 min	56	416	0 (-)	215	411	0 (-)	55	414	0 (-)
2 min	56	414	-2.1 (0.4)	215	411	0 (1.5)	55	409	-5.5 (2.3)
10 min	56	413	-2.4 (0.4)	214	413	2.1 (3.8)	55	411	-3.4 (0.5)
20 min	56	414	-1.4 (1.5)	215	412	1.3 (2.7)	54	412	-2.4 (1.2)
60 min	56	416	0.1 (3.7)	215	409	-1.6 (0.0)	55	409	-5.2 (-2.1)

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Study Report), pg. 475 (Table 8.5-6)
Key: Δ=change compared to same-day baseline
Note: N=Number of patients in the Treated Population; N1=number of patients with available data

ECGs signs were obtained at screening and at a single time point at least one hour after dosing at Visit 4 (Week 6) and Visit 8 (Week 14) in Trial C2. Change in QTc at Visit 4 and 8 is provided in Table 42. The observed changes in QTc were either balanced across treatment groups or not likely to be of clinical relevance.

Table 42. Change in QTc, Trial C2

	Placebo N=38		Epinephrine-HFA N=134		Primatene® Mist N=35	
	Value	Δ%	Value	Δ%	Value	Δ%
Screening	414±21	--	408±20	--	409±17	--
Visit 4 (Week 6)	411±23	-0.7%	409±19	0.2%	413±22	1.0%
Visit 8 (Week 14)	413±19	-0.2%	409±19	0.2%	*	*

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C2, Study Report), pg. 318 (Table 8-16)
*Data not available due to withdrawal of patients after the sunset of Primatene®
Key: Δ%=change from baseline (Screening)
Note: N=Number of patients in the Treated Population

The Applicant also provided an evaluation of the data for outliers in Trial C, i.e., patients with a change in QTc of greater than 40 or 50 ms. The results of this analysis are provided in Table 43. No notable imbalances are observed.

Table 43. Changes in QTc greater than 40 or 50 ms, Trial C

	Placebo N=61	Epinephrine-HFA N=248	Primatene® Mist N=64
	N1	N1	N1
	n (%)	n (%)	n (%)
Change in QTc > 40 ms	455	1822	466
	4 (0.9)	17 (0.9)	3 (0.6)
Change in QTc > 50 ms	455	1822	466
	1 (0.2)	6 (0.3)	2 (0.4)

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Study Report), pg. 479 (Table 8.5-7)
Note: N=Number of patients in the Treated Population; N1=number of ECG datapoints for change in QTc; n=number of events; %=percentage of ECG datapoints with event

In addition to the analysis of QT interval, ECG data from Trial C and C2 was evaluated for the presence of premature ventricular contractions (PVCs) and arrhythmia. A summary of PVC events observed in Trial C is provided in Table 44; there were a total of 13 PVC events (in 6 patients) observed in the treatment period, and all except for two events were reported for the epinephrine-HFA arm. While the imbalance between treatment arms is noted, the overall number of PVC events in Trial C is low. This is also the case for Trial C2, for which there were only two PVC events observed, and both events occurred at screening. No arrhythmias were reported for either Trial C or C2.

Table 44. PVC events, Trial C

	Placebo N=61	Epinephrine-HFA N=248	Primatene® Mist N=64
	N1	N1	N1

	n (%)	n (%)	n (%)
Baseline	115	458	117
	0	4 (0.9)	0
2 min	117	462	119
	0	1 (0.2)	0
10 min	116	462	118
	1 (0.9)	2 (0.4)	0
20 min	117	463	118
	0	1 (0.2)	0
60 min	116	463	119
	0	3 (0.6)	1(0.8)
Total	581	2308	591
	1 (0.2)	11 (0.5)	1 (0.2)

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-C, Study Report), pg. 482 (Table 8.5-9)
Note: N=Number of patients in the Treated Population; N1=number of ECG datapoints; n=number of PVC events; %=percentage of ECG datapoints with PVC event

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies/clinical trials were conducted apart from those already discussed earlier in this review.

7.4.6 Immunogenicity

As a small molecule, epinephrine is not anticipated to induce an immune response, and immunogenicity was not assessed.

7.5 Other Safety Explorations

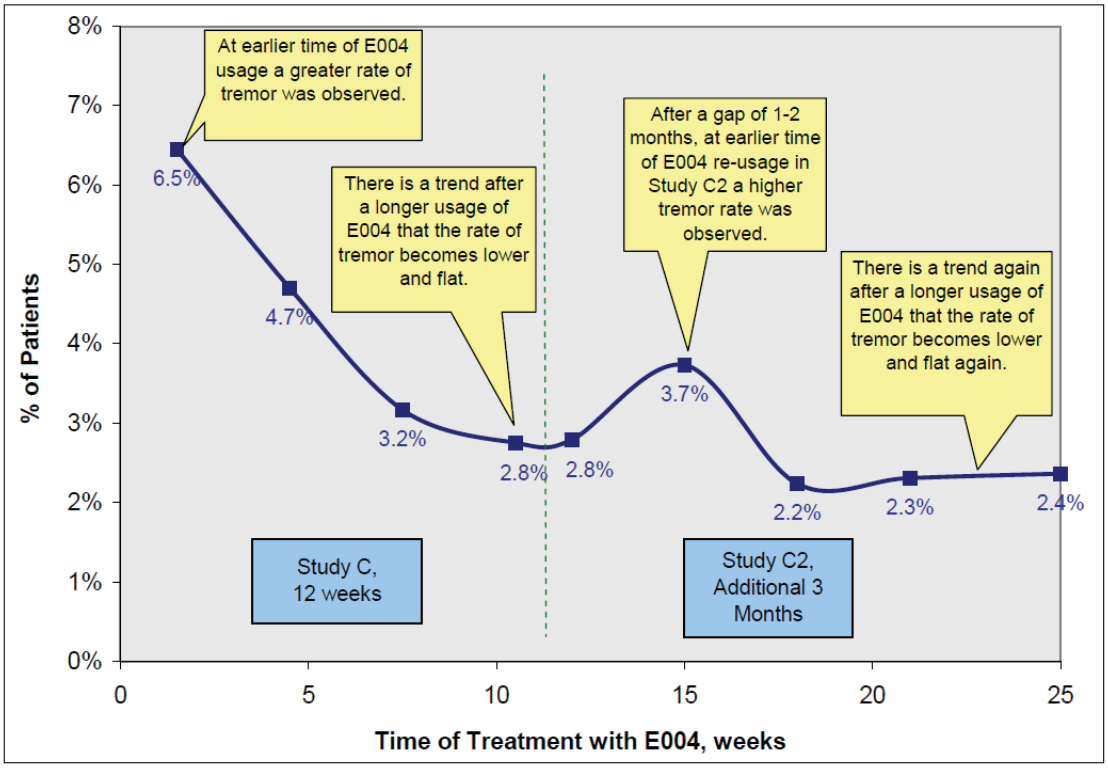
7.5.1 Dose Dependency for Adverse Events

Dose dependency for adverse events was not assessed in the phase 3 clinical program, as only a single dose was evaluated. Relevant safety findings from the dose-ranging trials are discussed in Section 4.4.2.

7.5.2 Time Dependency for Adverse Events

Time dependency was explored for tremor, which was the most commonly reported AE for patients treated with epinephrine HFA in Trials C and C2 combined. It appears that the incidence of tremor decreased over time, as is demonstrated in Figure 6.

Figure 6. Incidence of Tremor Over Time, Trials C and C2



Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.3 (ISS), pg. 75 (Figure ISS-7)
Note: E004=epinephrine HFA

7.5.3 Drug-Demographic Interactions

The submission does not include a specific analysis of AEs by demographic subgroup.

7.5.4 Drug-Disease Interactions

The submission does not include a specific analysis of AEs by disease severity, and no formal studies were conducted in patients with either renal or hepatic impairment.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No specific trials were conducted to assess for carcinogenicity in humans.

7.6.2 Human Reproduction and Pregnancy Data

Two pregnancies are reported for the phase 3 program, both for patients treated with epinephrine-HFA; details regarding the outcome of these pregnancies are not provided.

7.6.3 Pediatrics and Assessment of Effects on Growth

Adolescents were evaluated alongside adults in the phase 3 trials. In addition, the clinical development program included a single efficacy and safety trial (Trial D) in children 4 to 11 years of age. It should be noted that the Applicant is not seeking an indication for this age range. This stands in contrast to the reference product, Primatene® Mist, which had been approved down to four years of age.

The protocol for Trial D is summarized in Section 5.3, and the efficacy results are reviewed in Section 6. Included here is a discussion of the safety results from Trial D.

Exposure
The extent of exposure provided by Trial D, which had a 4-week treatment period, is summarized in Table 45.

Table 45. Summary of Exposure, Trials D

	Placebo N=35	Epinephrine-HFA N=35
Exposure, days		
Mean (SD)	26.3 (6.4)	27.0 (6.2)
Median	28	29
Min, Max	1, 32	1, 32

Source: Applicant's NDA 205-920 Submission January 24, 2014, Cover Letter, pg. 3 (Table 1)
Note: N=Number of patients in the Treated Population

The demographic characteristics and disposition of patients in Trial D are described in Sections 6.1.2 and 6.1.3, respectively, of this review.

Major Safety Results

There were no deaths or non-fatal SAEs reported for Trial D.

There were four patients who were discontinued from Trial D due to adverse events, two in each treatment group. The preferred term for the AE leading to withdrawal, in all four cases, was "asthma."

With regard to Adverse Events of Special Interest (AESI), tremor was reported for two patients (6%) in the epinephrine-HFA group, and zero patients in the placebo group. QTc prolongation was reported for a single patient (3%) in the epinephrine-HFA group, and for no patients in the placebo group. There were no reports of chest discomfort, chest pain, tachycardia, or heart rate increase for either arm of Trial D.

Supportive Safety Results

Common adverse events reported for 3% or more of patients in the epinephrine-HFA arm and greater than placebo in Trial D are provided in Table 46. The overall percentage of patients with AEs is balanced across treatment arms, and the frequency of individual events is low.

Table 46. Common Adverse Events Reported for ≥ 3% Patients in the Epinephrine-HFA arm and greater than placebo, by PT, Trial D

	Placebo N=35	Epinephrine-HFA N=35
All AEs, n(%)	14(40)	14 (40)
Tremor	2 (6)	0
Electrocardiogram QT prolonged	1 (3)	0
Gastroenteritis	1 (3)	0
Gastroenteritis viral	1 (3)	0
Nausea	1 (3)	0
Back pain	1 (3)	0
Myalgia	1 (3)	0
Cough	1 (3)	0
Erythema	1 (3)	0
Excoriation	1 (3)	0

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-D, Study Report), pg. 129 (Table 8-3), pg. 130 (Table 8-4)
Note: N=Number of patients in the Treated Population; n=number of occurrences of AE; %=n/N

Clinical laboratory assessments were performed at Screening and at the end of the 4-week treatment period (Visit 3). Change in mean values for potassium and glucose, which are of particular interest given epinephrine's known pharmacologic effects, are provided in Table 47. Change in mean values for the other chemistry and hematology parameters evaluated were reviewed and found to be unremarkable.

Table 47. Change in Mean Values for Chemistry Parameters, Trial D

	Placebo			Epinephrine-HFA		
	SCR *Mean ± SD*	EOS *Mean ± SD*	Δ	EOS *Mean ± SD*	SCR *Mean ± SD*	Δ
Glucose	86.2 ±10.1	85.0 ±8.4	-1.2	91.7 ±10.9	82.4 ±8.0	-9.3
Potassium	4.4 ±0.5	4.5 ±0.5	0.1	4.4 ±0.5	4.4 ±0.4	0.0

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-D, Study Report), pg. 176 (Table 8-10)
Key: EOS=end of study (i.e., Visit 3); SCR=screening; Δ=change

As can be seen from the data presented in Table 47, change in mean value was balanced across treatment arms for potassium, but not for glucose. Imbalances in both baseline value (92 vs. 86 for epinephrine-HFA and placebo, respectively), and change (-9 vs. -1 for epinephrine-HFA and placebo, respectively), are observed for glucose. The direction of the observed change for glucose (a decline) is contrary to the expected effect of epinephrine-HFA (hyperglycemia).

To further explore the impact of epinephrine-HFA on these laboratory parameters, change from same-day baseline at 15 and 120 minutes post-dose during Visit 3 was examined (Table 48).

Table 48. Change in Glucose and Potassium at 15 and 120 minutes post-dose during Visit 3, Trial D

	Placebo	Epinephrine-HFA
	% change	% change
Glucose		
15 min	7	21
120 min	0	4
Potassium		
15 min	-4	-3
120 min	-4	-3

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-D, Study Report), pg. 172 (Table 8-8)

The percent change in potassium over 120 minutes was similar between treatment arms. An imbalance is noted for percent change in glucose, particularly at the 15

minute time point (21% vs. 7% increase for epinephrine-HFA vs. placebo). The application notes that this imbalance was driven by data from a single study site.

Vital signs were evaluated over the 360 minutes after dosing at Visit 1 (Day 1) and Visit 3 (Day 28). Mean change in systolic blood pressure, diastolic blood pressure, and heart rate are provided in Table 49. Baseline diastolic blood pressure and heart rate were somewhat higher for the epinephrine-HFA arm compared to placebo. In general, mean change was balanced across treatment arms, with the exception of some of the time points for systolic blood pressure, where mean change for epinephrine-HFA exceeded that for placebo (e.g., 3 minutes post-dose on Day 1). This finding may warrant further exploration.

Table 49. Mean Change in Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate, Trial D

	Placebo N=35			Epinephrine-HFA N=35		
	N1	Mean	Mean Δ (Upper 95% CI)	N1	Mean	Mean Δ (Upper 95% CI)
Systolic Blood Pressure (mmHg)						
Visit 1 (Day1)						
0 min	35	101	0.0 (--)	35	102	0.0 (--)
3 min	35	100	-1.0 (1.2)	35	104	2.4 (4.8)
20 min	35	101	-0.7 (2.1)	35	102	0.4 (2.7)
60 min	35	102	0.7 (3.0)	35	102	-0.1 (2.7)
360 min	35	102	0.1 (2.6)	35	104	1.8 (4.3)
Visit 3 (Day 28)						
0 min	32	102	0.0 (--)	31	105	0.0 (--)
3 min	32	102	0.2 (2.4)	31	106	1.3 (3.8)
20 min	32	101	-1.3 (0.5)	31	105	-0.6 (2.2)
60 min	32	101	-1.5 (0.7)	31	104	-1.5 (0.9)
360 min	32	105	3.2 (5.5)	31	105	-0.5 (2.0)
Diastolic Blood Pressure (mmHg)						
Visit 1 (Day1)						
0 min	35	63	0.0 (--)	35	66	0.0 (--)
3 min	35	63	0.5 (2.6)	35	64	-2.0 (1.2)
20 min	35	64	1.1 (3.4)	35	66	-0.2 (2.3)
60 min	35	65	2.5 (4.3)	35	65	-0.9 (2.4)
360 min	35	63	-0.1 (2.2)	35	65	-1.5 (1.9)
Visit 3 (Day 28)						
0 min	32	63	0.0 (--)	31	66	0.0 (--)
3 min	32	63	0.8 (2.8)	31	66	-0.3 (2.3)
20 min	32	64	1.3 (3.5)	31	68	1.4 (3.7)
60 min	32	63	0.8 (3.4)	31	67	0.5 (3.3)
360 min	32	65	2.7 (4.9)	31	66	-0.7 (1.7)
Heart Rate (bpm)						
Visit 1 (Day1)						
0 min	35	74	0.0 (--)	35	80	0.0 (--)
3 min	35	74	0.4 (3.2)	35	79	-0.7 (2.6)

20 min	35	72	-1.8 (0.7)	35	77	-3.0 (0.3)
60 min	35	73	-1.0 (1.6)	35	79	-0.9 (2.4)
360 min	35	79	4.8 (8.8)	35	82	1.9 (5.3)
Visit 3 (Day 28)						
0 min	32	76	0.0 (--)	31	80	0.0 (--)
3 min	32	72	-3.3 (-0.5)	31	77	-2.5 (1.1)
20 min	32	75	-0.9 (2.0)	31	76	-3.3 (0.2)
60 min	32	76	0.3 (3.5)	31	76	-3.8 (-0.4)
360 min	32	82	6.1 (9.4)	31	83	3.3 (7.8)

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-D, Study Report), pg. 180 (Table 8-12)
Note: N=Number of patients in the Treated Population; N1=number of patients with available data

Electrocardiograms were obtained over the 60 minutes after dosing at Visit 1 (Day 1) and Visit 3 (Day 28) in Trial D. Mean change in QTc at the start and end of treatment is provided in Table 50. Baseline QTc was somewhat higher for the epinephrine-HFA arm compared to placebo on Day 1. Mean change was generally balanced across treatment arms, with some exceptions where the mean change for epinephrine-HFA exceeded that for placebo (e.g., 3 minutes post-dose on Day 1 and Day 28). This finding may warrant further exploration.

Table 50. Mean Change in QTc (ms), Trial D

	Placebo N=35			Epinephrine-HFA N=35		
	N1	Mean	Mean Δ (Upper 95% CI)	N1	Mean	Mean Δ (Upper 95% CI)
Visit 1 (Day 1)						
0 min	35	411	--	34	419	--
3 min	35	408	-3.9 (-0.6)	34	421	1.7 (6.7)
20 min	35	416	4.6 (8.8)	34	422	2.7 (7.0)
60 min	35	413	1.4 (5.1)	34	422	2.4 (8.2)
Visit 3 (Day 28)						
0 min	32	419	--	31	418	--
3 min	32	414	-4.8 (-1.2)	31	422	3.9 (8.7)
20 min	32	416	-2.4 (2.6)	31	415	-3.0 (2.0)
60 min	32	412	-6.4 (-1.3)	31	417	-0.9 (4.4)

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-D, Study Report), pg. 185 (Table 8-14)
Key: Δ=change compared to same-day baseline
Note: N=Number of patients in the Treated Population; N1=number of patients with available data

The Applicant also provided an evaluation of the data for outliers in Trial C, i.e., patients with a change in QTc of greater than 40 or 50 ms. The results of this analysis are provided in Table 51. A small numerical imbalance between treatment arms is observed, with more events reported for epinephrine-HFA. This finding may warrant further exploration.

Table 51. Changes in QTc greater than 40 or 50 ms, Trial D

	Placebo	Epinephrine-HFA

	N=35	N=35
	N1	N1
	n (%)	n (%)
Change in QTc > 40 ms	201	195
	1 (1)	5 (3)
Change in QTc > 50 ms	201	195
	0	1 (1)

Source: Applicant's NDA 205-920 Submission dated July 22, 2013, Section 5.3.5.1 (API-E004-CL-D, Study Report), pg. 188 (Table 8-15)
Note: N=Number of patients in the Treated Population; N1=number of ECG datapoints for change in QTc; n=number of events; %=percentage of ECG datapoints with event

In addition to the analysis of QT interval, ECG data from Trial D was evaluated for the presence of premature ventricular contractions (PVCs) and arrhythmia. No PVCs or clinically significant arrhythmias were noted by the Applicant.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The application does not specifically address the issue of drug abuse potential. The postmarketing experience with epinephrine-CFC, including that which is pertinent to abuse potential, is under review by the Division of Nonprescription Clinical Evaluation.

7.7 Additional Submissions / Safety Issues

The Applicant provided a 120-Day Safety Update on December 4, 2013. There were no new data for the completed trials submitted with the original NDA. The safety update reported that one additional trial, API-E004-CL-D2 ("Trial D2"), a crossover single-dose efficacy trial in 26 pediatric patients, is ongoing for statistical analysis and that formal data are not yet available. A high-level overview of adverse event data (blinded) for Trial D2 is provided in the safety update. A total of four adverse events are reported: viral upper respiratory tract infection, asthma, pyrexia, and influenza. These preferred terms are similar to those reported in the original application. Overall, no new or unexpected events are identified from the 120-Day Safety Update.

8 Postmarket Experience

While the proposed product is not currently marketed, FDA has conducted an analysis of the postmarketing experience for epinephrine-CFC. Final results of this review, conducted by the Division of Nonprescription Clinical Evaluation, are pending at this time.

9 Appendices

9.1 Literature Review/References

Two PubMed searches were performed by this Reviewer [1) search term: epinephrine HFA; no limits and 2) search term: epinephrine hydrofluoroalkane; no limits] were conducted on April 11, 2014. The first and second searched yielded 6 and 3 references, respectively. A brief review of these publications was performed. No new clinical safety signals were identified.

9.2 Labeling Recommendations

As the clinical review recommendation is against approval, labeling recommendations are not provided.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was held for this application on February 25, 2014. Four discussion and three voting questions were addressed. A brief summary of the deliberations of the committee, organized by question, is presented below.

1. **DISCUSSION:** Discuss the efficacy data for epinephrine inhalation aerosol 125 mcg per inhalation. Consider dose selection in the discussion.

   ***Committee Discussion**: The committee agreed that the data presented demonstrated efficacy for epinephrine inhalation aerosol 125 mcg per inhalation when used as directed. However, the committee acknowledged that this data was produced in a well-controlled study environment and that these results may not be consistent in a real use setting. Several committee members expressed that the written submissions from the public illustrated the strongest evidence that the product would not be used as directed. The committee highly recommended the sponsor conduct a "real use" study.*

2. **DISCUSSION:** Discuss the safety profile of epinephrine inhalation aerosol 125 mcg per inhalation for the over-the-counter (OTC) setting.

   ***Committee Discussion:** The committee did not come to a consensus regarding whether epinephrine inhalation aerosol 125 mcg per inhalation for the over-the-counter (OTC) setting is safe. Many of the committee members agreed that the OTC*

setting would not be safe based on the following reasons: (1) patients will not be able to adequately self-assess the severity of their condition; (2) patients may undertreat or over-treat their condition and (3) there is limited longitudinal data to illustrate long term use effects. On the contrary, several panel members made reference that the CFC product that was recently removed from the market was not viewed as an unsafe drug product and was available for several years. Panel members also noted that the data presented by the sponsor and FDA was reassuring regarding the safety profile despite its limitations.

3. **DISCUSSION:** Discuss the impact of device performance of epinephrine inhalation aerosol 125 mcg per inhalation on both efficacy and safety.

   Committee Discussion: *The committee's discussion on the impact of device performance of epinephrine inhalation aerosol 125 mcg per inhalation on both efficacy and safety was limited due to the discussion that transpired during questions #1 and #2. However, a few panel members expressed some concerns due to the lack of actual use data, limited data on device dropping studies and device cleaning requirements. One panel member expressed concerns that since this product could be purchased anywhere if approved for the OTC setting, it would limit the ability of a health care provider to adequately explain the proper way to use the device to ensure adequate dosing.*

4. **VOTE:** Do the efficacy data provide substantial evidence for the OTC use of epinephrine inhalation aerosol 125 mcg per inhalation in adults and children 12 years of age and older for the proposed indication, "the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath"?

   Vote: YES = 14 NO = 10 No Vote = 1

   a. If not, what further data should be obtained?

   Committee Discussion: *A narrow majority of the committee agreed that the efficacy data provided substantial evidence for the OTC use of epinephrine inhalation aerosol 125 mcg per inhalation in adults and children 12 years of age and older for the proposed indication, "the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath". Several committee members who voted "Yes" based their decision on the adequate efficacy and safety data presented. Other panel members who voted "Yes" acknowledged that epinephrine is an effective bronchodilator and has been available for use for a very long time. The committee members who voted "No" were concerned about the lack of "real use" data and limited data submitted for patients 12-18 years of age. Several panel members indicated that they voted "No" based on the wording of the question and would have voted "Yes" if the question just asked if*

epinephrine is an effective bronchodilator. In addition, the panel members expressed that the remaining portion of the question was not adequately addressed regarding the age group of 12-18 years old or about the symptomatic relief. Overall the panel suggested the following additional studies: (1) actual use; (2) efficacy; and (3) before and after studies on specific indications listed on the label (i.e. wheezing tightness of chest, and shortness of breath). One panel member was unable to stay for the entire meeting and was counted as a "No Vote".

5. **VOTE:** Has the safety of epinephrine inhalation aerosol 125 mcg per inhalation for OTC use in intermittent asthma been adequately demonstrated??

Vote: YES = 7 NO = 17 No Vote = 1

a. If not, what further data should be obtained?

Committee Discussion: *The majority of the committee agreed that the safety of epinephrine inhalation aerosol 125 mcg per inhalation for OTC use in intermittent asthma was not adequately demonstrated. Several committee members who voted "No" expressed their concerns regarding the lack of safety data presented. One panel member expressed concerns about the lack of long-term safety data in an unregulated environment. Another panel member expressed a concern regarding the patients' inability to adequately assess the severity of their asthma. The committee members who voted "Yes" were satisfied with the safety data presented. In addition, many noted the long standing safety history with the CFC product. Overall, the panel suggested the following additional studies/data: (1) actual use; (2) efficacy studies on ages 12-18 years old; (3) long-term follow up; (4) device clogging; (5) albuterol comparator; (6) comorbidity studies; and (7) handling/dropping of device. One panel member was unable to stay for the entire meeting and was counted as a "No Vote".*

6. **DISCUSSION:** Discuss the proposed Drug Facts label and Consumer Package Insert.

Committee Discussion: *The committee made the following recommendations for the proposed Drug Facts label and Consumer Package Insert:*

- *Clearly define what "Priming" means (this information should be listed as one of the first items on the label)*
- *Clearly identify the various parts of the inhaler/device*
- *With regards to the dose indicator on the device, using the word "spray" as a noun versus a verb would provide a better understanding of how many doses are actually available for use*
- *Remove the word "daily" as it gives the impression that this product should be used on a daily basis*

7. **VOTE:** Is the risk/benefit profile of epinephrine inhalation aerosol 125 mcg per inhalation supportive of OTC use for the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath in adults and children 12 years of age and older?

   Vote: YES = 6 NO = 18 No Vote = 1

   a. If yes, do you have additional comments or recommendations for labeling?

   b. If not, what further data should be obtained?

   Committee Discussion: *The majority of the committee did not agree that the risk/benefit profile of epinephrine inhalation aerosol 125 mcg per inhalation supported OTC use for the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath in adults and children 12 years of age and older. Several committee members voted "No" due to safety concerns previously discussed. A few panel members expressed concerns regarding the device and the use of the name "Primatene". The committee members who voted "Yes" were satisfied with the data presented and noted the longstanding history of the product's use. One panel member was unable to stay for the entire meeting and was counted as a "No Vote".*

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/s/

JENNIFER R PIPPINS
04/12/2014

SUSAN L LIMB
04/14/2014