CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205920Orig1s000

OTHER REVIEW(S)

Labeling Review Addendum-1 for [redacted] (b) (4)

Resubmission #2

SUBMISSION DATES:	September 11, 2018 October 9, 2018 October 17, 2018 October 24, 2018 October 25, 2018
NDA/SUBMISSION TYPE:	205920/ Class 2 resubmission
ACTIVE INGREDIENTS:	Epinephrine 0.125 mg/inhalation
DOSAGE FORM:	Aerosol, metered
SPONSOR:	Armstrong Pharmaceuticals, Inc. 25 John Road Canton, Massachusetts 02021 Gisela Sharp Senior Manager, Regulatory Affairs (909) 980-9484, ext. 2016
REVIEWER:	Michelle D. Walker, PhD IDS Pharmacologist, DNDP
TEAM LEADER:	Steven Adah, PhD Lead Chemist, DNDP
PROJECT MANAGER:	Helen Lee, PharmD Regulatory Project Manager, DNDP

I. BACKGROUND

The labeling for Primatene Mist included reference to a website. Websites are considered labeling and because it was not submitted with the original package, the content of the website was requested in an Information Request (IR). The sponsor submitted the website content on September 11, 2018.

The review team edited the outer container, immediate container, actuator, consumer information (CII), and website labeling and an IR was issued on October 5, 2018 to address issues with each

of the labeling items. The sponsor responded to the information request with the October 9, 2018 submission via email. Following issuance of another IR on October 17, 2018, the sponsor submitted an updated outer container label with revised DFL font specifications on October 17, 2018.

Subsequent to the October 17 response, additional deficiencies in the outer carton label were identified which were shared with the sponsor by a telephone discussion held on October 19, 2018 with a follow up email on October 22, 2018. A revised outer carton label was submitted on October 24, 2018. During review of the revised carton label, it was evident the sponsor missed some of the deficiencies identified in October 22 email. These issues were pointed out to the sponsor who, provided a revised outer carton label on October 25, 2018.

This review is conducted in chronological order.

The sponsor submitted labeling listed in the table below:

Submitted Labeling	Date(s) submitted
160-spray, 11.7 g outer container label	October 9, 2018, October 17, 2018, October 24, 2018 and October 25, 2018
160-spray, 11.7 g immediate container label	October 9, 2018
Actuator label	October 9, 2018
Consumer information insert	October 9, 2018
Website content	September 11, 2018 and October 9, 2018

II. REVIEWER'S COMMENTS

The following comments are in response to the October 9 and 17 submissions

A. (b) (4) 160-spray Outer Container

1. Area outside of the PDP

a. The top panel has been revised to state the following:

See Insert and Side Panels for Special (b) (4) on:
- Activating your New Inhaler
- Dosing with your New Inhaler
- Using Spray Indicator

Reviewer's comment: *This is acceptable. These are the statements recommended by FDA in the IR submitted to the sponsor on October 5, 2018.*

2. PDP labeling

a. As requested, (IR dated October 5) the PDP statement "Suspension: [redacted] (b) (4)" has been revised to read "Suspension: [redacted] (b) (4)"

Reviewer's comment: *This is acceptable.*

3. Outer Carton Drug Facts Label

a. The DFL font specifications did not meet the requirements of 21 CFR 201.66. The sponsor was directed (IR dated October 16) to revise the DFL to comply with 201.66.

The following DFL font specifications were submitted:

Drug Facts 10 pt
Drug Facts (continued) 8 pt
Headings 9 pt
Drug Facts body text 7 pt
Bullet 5 pt
Barline 2.5 pt
Hairline 0.5 pt
Leading space between lines 7.5 pt
32 characters per inch

Reviewer's comment: *This is acceptable. The font specifications now meet the requirements under 21 CFR 201.66.*

b. The subsection **If pregnant or breast-feeding** within the Warnings heading section was relocated to appear just above the ***Questions or comments?*** section.

Reviewer's comment: *This is acceptable. This sequence is in compliance with 21 CFR 201.66 (c)(5).*

c. The ***Directions*** section was slightly modified to comply with the bullet formatting requirement of 21 CFR 201.66 (d)(4), and to ensure all sections have the same type and style of bullets. Specifically, the subheading ***Each Time You Dose*** [redacted] (b) (4) was modified to the bulleted 5 point solid square format.

Reviewer's comment: *This is acceptable. The consumer can easily follow the directions in bulleted sequential order and the DFL is now compliant with 201.66* [redacted] (b) (4)

d. Under ***Directions:*** in the instruction under the additional subheadings are edited. The edited directions are below:

Each Time You Dose:
- Remove red cap (if attached).
- Shake then Spray into the air 1 time.
- Exhale completely, place inhaler in mouth.
- Inhale deeply while pressing down on top of inhaler, then continue the deep breath.
- Hold breath as long as possible, exhale.
- Wait 1 minute. If symptoms are not relieved, repeat steps above.

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 the mouthpiece for 30 seconds.

Reviewer's comment*: This is acceptable. The sponsor added "(if attached)" to the first step. The language used is in consistent with that recommended by FDA in the IR.*

B. 160-spray Immediate Container Label

1. Under the statement of identity, the statement reads "For Oral Inhalation Only." The text of the word "Only" is written in red font.

Reviewer's comment: *This is acceptable. In the October 5 IR, FDA directed the sponsor to add the word "Only" to be consistent with that statement on the PDP.*

2. Under **Directions:** the instructions are edited. The statement is written as follows:

"Do not use more than directed. Adults and children 12 years of age and over: shake then spray into the air one time before each inhalation. 1 to 2 inhalations for each dose. Start with one inhalation, wait at least 1 minute. If not relieved, shake then spray into the air one time and take a second inhalation."

"(b) (4)" is written in red font. The sponsor stated that the font color was changed to be consistent with actuator and CII labeling.

Reviewer's comment: *This is acceptable. In the October 5 IR, FDA directed the sponsor to use this language.*

C. Actuator Label

The instructions on the actuator are edited to the following:

Dose, A dose is 1-2 inhalations
1. Shake then spray into the air one time
2. Inhale

Wash, After Each Day of Use
1. Remove the red cap and container.
2. Run water through the mouthpiece for 30 seconds.
3. Shake off excess water.

Reviewer's comment: *This is acceptable. In the October 5 IR, FDA directed the sponsor to use this language.*

D. Consumer Information Insert (CII)

1. The asthma alert is placed under the red box containing the indication for Primatene Mist and above the Important Information box.

   Reviewer's comment: *This is acceptable. In the October 5 IR, FDA directed the sponsor to include the asthma alert on the CII to ensure that consumers have as much access to the asthma alert as possible.*

2. In the **Important Information** box, an instruction was changed to state, "Shake then Spray into the air 1 time before each inhalation." The font color for "Shake then Spray" is written in red font.

   Reviewer's comment*: This is acceptable. In the October 5 IR, FDA directed the sponsor to use this language.*

3. In the **Important to Know** box, a statement (b) (4) is removed.

   Reviewer's comment: *This is acceptable. In the October 5 IR, FDA directed the sponsor delete the statement since FDA is requiring that a priming step be done before each inhalation.*

4. In the **Important to Know** box, the instruction to wash the inhaler is changed to after each day of use (b) (4)

   Reviewer's comment: *This is acceptable. In the October 5 IR, FDA directed the sponsor the change the washing frequency instruction.*

5. The section instructing the consumer [redacted] (b) (4) .

   Reviewer's comment: *This is acceptable. In the October 5 IR, FDA directed the sponsor delete this section since FDA is requiring that a priming step be done before each inhalation.*

6. Under the **Step-By-Step Instructions** section, the font color of Panel A. Activating Your Inhaler is changed to red from [redacted] (b) (4)

   Reviewer's comment: *This is acceptable. In the October 5 IR, FDA requested that the sponsor change the font color so that it is consistent with colors on the actuator label.*

7. The font color of Panel B. **Activating Your Inhaler** is changed to green from [redacted] (b) (4)

   Reviewer's comment: *This is acceptable. In the October 5 IR, FDA requested that the sponsor change the font color so that it is consistent with colors on the actuator label.*

8. Under **B. Dosing with Your Inhaler**, a general statement is edited as follows:
   "For every inhalation: Shake then Spray (in red font) → Inhale → Wait"

   Reviewer's comment*: This is acceptable. In the October 5 IR, FDA directed the sponsor to use this language.*

9. For the shaking instruction, title of the section is "Shake then Spray Into the Air".

   Reviewer's comment: *This is acceptable. In the October 5 IR, FDA directed the sponsor to use this language.*

10. In section B, under the **Shake the Spray Into the Air** panel, the instruction is edited to "Shake then Spray into the air 1 time to mix the medicine (Figure D)."

    Reviewer's comment*: This is acceptable. In the October 5 IR, FDA directed the sponsor to use this language.*

11. In section B, the warning statement is edited to "Shaking and spraying the inhaler are critical".

Reviewer's comment*: This is acceptable. In the October 5 IR, FDA directed the sponsor to use this language.*

12. Under the **Wait at Least 1 minute** section, there an instruction is edited to state "If symptoms are not relieved after at least 1 minute (Figure G), take a second inhalation by repeating steps 2 to 7 above."

Reviewer's comment*: This is acceptable. In the October 5 IR, FDA directed the sponsor to use this language.*

13. As with other labeling, in section C, **Washing Your Inhaler**, the washing instruction is changed to wash after each day of use.

Reviewer's comment: *This is acceptable. In the October 5 IR, FDA directed the sponsor to change the wash frequency* (b) (4) *to daily.*

E. Website

1. The images of the mouthpiece and the PDP of the outer container are displayed throughout the website and they have been revised to reflect the updated labeling requested in the October 5 IR.

   Reviewer's comment*: This is acceptable.*

2. The sponsor universally updated the name (b) (4) to "Primatene MIST" throughout the website.

   Reviewer's comment*: This is acceptable, since Primatene MIST is the DMEPA-approved brand name of the product.*

3. The ***Directions*** in the website DFL are updated to mirror the complete DFL on the outer container.

   Reviewer's comment*: This is acceptable.*

4. The videos on page 4 were updated to reflect changes in labeling. The sponsor changed the colors of the instruction video headings to match colors of the corresponding sections on actuator label.

   Reviewer's comment*: This is acceptable.*

5. The webpage displaying the consumer information insert is updated to mirror the revised CII label.

Reviewer's comment: *This is acceptable.*

6. On page 6, under the heading "The New Primatene MIST," there is a sentence mentioning the previous Primatene Mist product. The statement was edited to "The new Primatene Mist is a CFC-free metered dose inhaler (MDI) that uses epinephrine as its active ingredient, the same active ingredient used in the previous Primatene Mist. The new Primatene Mist MDI propelled by hydrofluoroalkane (HFA 134a) works differently from the old Primatene Mist Inhaler containing CFCs. Be sure to read the Consumer Information Insert for detailed directions on how to correctly use your Primatene Mist metered dose inhaler."

   Reviewer's comment: *This is acceptable. This verbiage is consistent with that recommended by FDA in the October 5 IR.*

7. On page 6, under the heading "Preparing Primatene MIST for the First Time Use", the numbering for an instruction that states, "d. Shake then test spray into the air." is changed to "c" from "d". A statement was edited to "You must repeat both actions 4 times to activate your new inhaler." to match the statement on the CII.

   Reviewer's comment: *This is acceptable.*

8. On page 6, to be consistent with recommendations of the other labeling, the heading titled [redacted (b) (4)]" is changed to "New Requirements to Shake then Spray into the Air 1 Time Before Each Use."

   Reviewer's comment: *This is acceptable. In the October 5 IR, FDA directed the sponsor to use this language.*

9. On p. 6, the section [redacted (b) (4)] was deleted.

   Reviewer's comment: *This is acceptable. In the October 5 IR, FDA directed the sponsor delete this section since FDA is requiring that a priming step be done before each inhalation.*

10. On p. 7, there is a section on washing instructions for the mouthpiece. The instruction says to wash inhaler after [redacted (b) (4)] The washing instruction is changed to wash after each day of use.

    Reviewer's comment: *This is acceptable. In the October 5 IR, FDA directed the sponsor to change the wash frequency [redacted (b) (4)] to daily.*

11. On p. 10, the customer service hours were updated to 7 am – 5 pm PST to match that on other labeling.

Reviewer's comment: *This is acceptable.*

On October 19, 2018, FDA requested a teleconference with the sponsor to discuss additional labeling concerns. Specifically, the DFL order did not meet the requirements of 21 CFR 201.66 and the DFL was not on consecutive panels on the outer carton. FDA requested the sponsor revise the label to which the sponsor agreed. FDA also noted, other minor edits would be forthcoming by email. Those additional edits were sent on October 22nd.

The edits included formatting errors, e.g. removing punctuation, letter capitalization, spacing of hairlines (DARRTS, dated 10/22/18). FDA also requested the location of the expiry date and lot number as that information was not present on the revised carton.

On October 24, 2018, the sponsor responded with new labeling, addressing most our recommendations. A few of the changes that FDA noted in the October 22nd IR were not addressed by the sponsor, so FDA sent another IR noting the remaining edits that needed to be addressed and requested that the sponsor submit an updated outer container label (DARRTS, dated 10/25/18). On October 25, 2018, the sponsor submitted new labeling, which addressed all of FDA's remaining recommendations.

The DFL panel is now on consecutive panels and the DFL contents are in order as outlined in 21 CFR 201.66. The sponsor identified the lot number and expiry date would appear on the top panel of the box just above the website. The edits requested by FDA have all been addressed.

All labeling issues for Primatene have been addressed. The sponsor will be asked to submit clean labels, without markup, for final approval. A specific request will be to remove the red lines on the outer carton label that are used to distinguish the borders of the outer carton panels.

III. RECOMMENDATIONS

Issue an APPROVAL letter to the sponsor and request that the sponsor submit final printed labeling for the Primatene® MIST identical to the labels listed in the table below:

Submitted Labeling	Date(s) submitted
160-spray, 11.7 g outer container label	October 25, 2018
160-spray, 11.7 g immediate container label	October 9, 2018
Actuator label	October 9, 2018

Consumer information insert	October 9, 2018
Website content	October 9, 2018

The labeling must be in the "Drug Facts" format (21 CFR 201.66), where applicable.

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

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

/s/

MICHELLE D WALKER
10/29/2018

STEVEN A ADAH
10/29/2018

HUMAN FACTORS STUDY REPORT AND LABEL, LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 19, 2018
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 205920
Product Name and Strength:	Primatene Mist (Epinephrine) Inhalation Aerosol, 125 mcg per inhalation
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Over-the-Counter (OTC)
Applicant/Sponsor Name:	Armstrong Pharmaceuticals, Inc. (Armstrong)
FDA Received Date:	May 7, 2018 and August 24, 2018
OSE RCM #:	2018-1165 and 2018-1222
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

This review responds to a Division of Nonprescription Drug Products (DNDP) consult requesting DMEPA to evaluate the human factors (HF) validation study report results, the proposed Instructions for Use (IFU), actuator label, container label, and carton labeling for Primatene Mist (epinephrine) inhalation aerosol (NDA 205920) for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT BACKGROUND AND REGULATORY HISTORY

The proposed over-the-counter (OTC) product Primatene Mist (Epinephrine) inhalation aerosol is a single-ingredient combination product with an inhaler device constituent for use in the temporary relief of mild symptoms of intermittent asthma in adults and children age 12 and older.

Primatene Mist (epinephrine) inhalation aerosol was approved on November 8, 1967, under NDA 016126 and originally marketed by Wyeth Consumer Healthcare. Armstrong was the contract manufacturer of Primatene Mist from 2004 to 2008 and acquired the product from Wyeth on July 8, 2008. Armstrong marketed the product until December 31, 2011, when it was withdrawn from distribution due to the phase out of chlorofluorocarbons (CFC) outlined in the Montreal Protocol.

Since then, Armstrong has re-formulated the epinephrine inhalation aerosol using HFA-134a (hydrofluoroalkane) as the propellant. On July 20, 2013, Armstrong submitted the re-formulated epinephrine HFA inhalation aerosol for review under NDA 205920. On May 22, 2014, the application received a Complete Response (CR) letter. On June 28, 2016, the Applicant resubmitted their application. The application received a CR letter on December 23, 2016. The December 23, 2016 CR stated that the human factors (HF) validation (G3) study failed to demonstrate that the Primatene Mist user interface supports the safe and effective use of the product by intended users for the proposed product's OTC use and recommended they optimize the user interface and validate the changes to the interface in an HF study.

Armstrong submitted an HF validation (G4) study protocol for review on November 8, 2017 under NDA 205920, and we provided recommendations to improve the protocol.[a]

On May 7, 2018, Armstrong resubmitted NDA 205920 for the proposed Primatene Mist, including the HF validation (G4) study results.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

[a] Jones, G. Human Factors Validation Study Protocol Review for Primatene Mist NDA 205920. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 02. OSE RCM# 2017-2312.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – N/A
Labels and Labeling	G and H

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The sections below provide an assessment of the HF validation (G4) study results, which includes the study design and use errors observed with critical tasks, and our assessment of the Instructions for Use (IFU), actuator label, container label, and carton labeling.

3.1 HUMAN FACTORS VALIDATION (G4) STUDY

The preceding HF validation (G3) study failed to demonstrate that the user interface supports safe and effective use of the proposed product by intended users for OTC use. Armstrong stated in their current submission that they mitigated failures seen in the G3 study by a) adding an actuator label on the mouthpiece of the inhaler device as advised in the December 23, 2016 CR letter, b) performing additional bench studies, and c) revising language and graphics on the proposed labeling (e.g., IFU was revised to a single page). They further indicated in the submission that the IFU was updated to align with the findings from the bench studies. Armstrong also conducted formative HF studies to evaluate these labeling changes.

We note that Armstrong addressed our recommendations for the HF validation (G4) study protocol and provided granular HF study data as requested.

Summary of the Study Design:

The HF validation (G4) study evaluated if the newly proposed user interface, including the entire product packaging using a placebo-filled inhaler device, supports the safe and effective use by the intended users for the proposed OTC environment.

The study was conducted in 45 participants who were untrained:

- 30 adults (15 inhaler experienced asthma participants and 15 inhaler naïve non-asthma participants)

- 15 adolescents (8 inhaler experienced asthma participants and 7 inhaler naïve non-asthma participants)
- Of the adult participants:
    - inhaler experienced asthma participants, 6/15 (40%) were low literacy[b]
    - inhaler naïve non-asthma participants, 6/15 (40%) were low literacy
    - overall total of 12/30 (40%) adults were low literacy
- Of the adolescent participants:
    - inhaler experienced asthma participants, 5/8 (62.5%) were low literacy
    - inhaler naïve non-asthma participants, 5/7 (71%) were low literacy
    - overall total of 10/15 (67%) adolescents were low literacy

Participants performed unaided simulated tasks for the following 3 critical tasks:

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

The minimal acceptance criteria for each of the simulated critical tasks are:

1) Task 1: initial prime – user must shake and spray into the air 1 time to successfully prime the inhaler for the first time.
2) Task 2: routine use (dosing) – user must shake the inhaler before inhaling to successfully take a dose.
3) Task 3: washing procedure – user must rinse water through either end of the mouthpiece for at least 2 seconds to successfully complete the washing procedure.

Although Armstrong included the task "washing procedure" as a part of the HF validation (G4) study testing, Armstrong did state that the task "washing procedure" is not a critical task based on the submitted bench studies.

After the simulation testing, participants were asked 1 knowledge probe question and 1 comprehension question based on information in the IFU:

[b] Appendix A of the HF validation (G4) study report did not provide which participants Armstrong considered to be low literacy based on the participants' REALM literacy score. Armstrong identified the participants with low literacy in the Response to Information Request received on 08/24/2018. \\cdsesub1\evsprod\nda205920\0075\m1\us\narrative-response.pdf

- Knowledge probe: participants were asked what to do if your inhaler had not been used in over 2 weeks and you need to dose with it (correct response is to reactivate the inhaler by shaking and spraying one time)
- Comprehension question: participants were asked to read the IFU section related to using the inhaler device that is still wet after washing and were asked to restate what they read in their own words (correct response is to shake off excess water before dosing)

For the knowledge probe question, Armstrong classified "reactivation after no use for 2 weeks" as a critical task.

3.2 RESULTS AND ANALYSIS

Table 2 below provides a summary of the failures/use errors and close calls/use difficulties observed in the HF validation (G4) study, Armstrong's root cause analysis and mitigation strategies for the observations, and DMEPA's analysis and recommendations.

Table 2. Summary and Analysis of Primatene Mist Human Factors Validation(G4) Study Results

Task	Subtasks	Number of Use Errors and Description Number of Use Difficulties and Description	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and General Recommendations
Task 1: Initial Prime – Activating the Inhaler **IFU label states: "Shake then test spray into the air" "You must repeat both actions 4 times to activate your new inhaler"**	**Subtask #3: Shake and Spray 4 times (critical)**	**<u>3 Use Errors</u>:** **Did not shake and spray 4 times.** 1) (b) (4) (Adult Asthma Inhaler Experienced) shook 1 time and sprayed 1 time. She did not refer to the instructions during her activation attempt and stated that she saw spray come out of the nozzle and assumed it was fine. This is how she confirms activation of her current inhaler (page 87). 2) (b) (4) (Healthy Adult Inhaler Naïve) performed 4 shakes and 2 sprays. **(Low literacy)** First sprayed with the cap on, then uncapped the inhaler and shook it once. then recapped it and shook a second time. then consulted the IFU, uncapped the device, shook and then sprayed once into the air, shook again, then recapped the inhaler (page 87). 3) (b) (4) (Juvenile Asthma Inhaler Experienced) shook 1 time and then sprayed 4 times in rapid succession. She did not refer to the instructions during her activation attempt. The debrief confirmed that the participant used their past inhaler experience and deviated from the instructed procedure. (b) (4) attributed the error by saying, "I did it because I am used to doing it that way." (page 88) **(Low literacy)**	All participants met the minimal acceptance criteria to at least shake then spray 1 time. The deviations were influenced by prior inhaler experience or the participant not paying enough attention to the intended procedure. No mitigation is required as all participants knew how to activate, attempted to activate and performed the task within an acceptable range (page 88).	No mitigation proposed.	Based on our discussions with our CMC colleagues, we understand that shaking and spraying the inhaler only 1 time results in a potential deviation and suboptimal dose; however, labeled directions allow for a second inhalation that would provide an optimal dose. Furthermore, deviations of 2 shakes and 2 sprays and 3 shakes and 3 sprays would not result in dose deviations leading to an over or underdose. The DNDP review team also finds initial priming with shake and spray only 1 time to be clinically acceptable. We also note that Armstrong has optimized the user interface to the extent possible by adding instructions to the actuator label. As such, we find the residual risks acceptable, and have no recommendation.

Task	Subtasks	Number of Use Errors and Description Number of Use Difficulties and Description	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and General Recommendations
Task 2: Dosing – Routine Use **IFU label states: "Shaking inhaler is critical"**	**Subtask 2: Shake inhaler (critical)**	**<u>2 Use Errors</u>:** **Did not shake inhaler prior to dosing (inhaling)** 1) (b) (4) (Adult Asthma Inhaler Experienced) stated in the error debrief that s/he had just shaken it 4 times in the prior task (activating the inhaler) and thought it was ready to go. 2) (b) (4) (Healthy Juvenile Inhaler Naïve) said s/he forgot and had shaken it (4 times and sprayed 4 times) during activation that just preceded this task, so s/he did not shake it prior to dosing (page 96).	Both errors are attributed to a study artifact as participants were influenced by the fact that they had shaken the inhaler during priming/activation task earlier in the session (page 130). This influenced both participants (per their debrief statements) to not shake the inhaler prior to dosing. Per Armstrong, it would be acceptable to dose immediately after activation without additional shaking, because the device was just shaken and sprayed out 4 times (page 96).	All labeling (carton, IFU, actuator label) already clearly state and illustrate to shake before inhaling. No mitigation proposed.	We agree with Armstrong's root cause analysis and discussion that the 2 use errors seen in the study were due to study artifacts. We have no recommendation based on the observations of this task performance in the study.

Task	Subtasks	Number of Use Errors and Description Number of Use Difficulties and Description	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and General Recommendations
Task 3: Washing the inhaler **IFU label states: "Remove container by firmly grasping and pulling out the container, then set aside"**	**Subtask 2: Remove container (critical)**	**<u>1 Use Error</u>:** **Did not attempt to remove container prior to washing** (b) (4) (Adult Asthma Inhaler Experienced) did not remove the container before washing the mouthpiece, but ran water through the mouthpiece end and shook off all excess water after rinsing (page 131). In addition, no water was exposed to the container side of the actuator, and the participant rigorously shook the inhaler after washing (b) (4) stated in his debrief, "I normally clean mine that way." (b) (4) was asked to repeat the washing task at the end of the study and demonstrated that they could remove the container prior to washing (page 103).	This error is attributed to their prior experience. During the failure debrief (b) (4) stated, "I normally clean mine that way" (page 131). This deviation is not clinically important as the participant did rinse the nozzle of the mouthpiece and shook off excess water, and did not harm the inhaler in the process (page 103). Applicant also indicates there is no safety impact (page 135).	The participant cleaned the mouthpiece and used their prior experience to influence how to clean the Primatene inhaler. The residual risk cannot be mitigated further as the IFU was demonstrated to be effective in educating all other users to remove the container prior to cleaning the mouthpiece (page 131). No mitigation proposed.	Based on the observations of this task performance in the study, we have no recommendations. We understand from our CMC colleagues that the new bench study data showed that not washing the inhaler over a 20-day period does not lead to the inhaler clogging. However, continuous use of the inhaler beyond 7 days without washing may result in dispensing of an inconsistent dose. Furthermore, our CMC colleagues find that the conservative approach of washing the inhaler once daily is the best scenario for this product because daily washing allows for dispensing of a consistent dose. The DNDP review team also finds washing the inhaler every day after use is clinically preferable. Thus, we do not object with the DNDP review team's recommendations to change the frequency of washing the inhaler.

Task	Subtasks	Number of Use Errors and Description Number of Use Difficulties and Description	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and General Recommendations
		2 Use Difficulties: **Difficulty Removing Container** Observed having difficulty removing the container from the mouthpiece but were ultimately successful after a few attempts (page 131). 1) (b) (4) (Healthy Juvenile Inhaler Naïve) took multiple attempts to remove the container, but ultimately succeeded (b) (4) is younger in age (13 years old), had weak hand strength, and stated to the moderator that she had very sweaty hands (out of nerves) when performing the task. (b) (4) was ultimately successful in removing the container but stated if she could not do it she would get her parent to help. At the end of the study (b) (4) was asked to repeat this task and demonstrated that she could remove the container without difficulty (page 104). 2) (b) (4) (Juvenile Asthma Inhaler Experienced) struggled to remove the container as he had recent arm surgery, which severely limited his strength of this dominant hand. After a few attempts (b) (4) was successful in removing the container from of the inhaler without any prompting from the moderator (page 104). **(Low literacy)**	(b) (4) difficulty was associated with her age (13 years old), more limited hand strength and (b) (4) stated she has very sweaty hands when attempting the task. This made it more difficult to grasp the container and pull it out. At the end of the study (b) (4) was asked to repeat the task of removing the container from the mouthpiece and did so successfully on their own with no difficulty. (b) (4) difficulty was due to the fact that the juvenile recently had arm surgery and his arm was in a sling during the study. (b) (4) had limited hand strength but demonstrated he could remove the container (page 131).	Both participants were ultimately successful in removing the container after a few attempts. In the situation where the child could not remove the container, it is presumed they would ask a parent for support (page 131). No mitigation proposed.	

Task	Subtasks	Number of Use Errors and Description Number of Use Difficulties and Description	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and General Recommendations
Knowledge Probe Question: *Participants were asked the question* "What should you do if you have not used your inhaler in a while, say it's been sitting in your drawer and it's been at least two weeks since your last used it? And, now you want to use it again." ○ *Correct answer is to reactivate by shaking and spraying into the air 1 time before dosing*		**2 Use Errors:** **1) Failure to identify the need to reactivate inhaler by shaking and test spraying at least once:** (b) (4) (Healthy Adult Inhaler Naïve) stated to wash the inhaler (page 132). **(Low literacy)** (b) (4) was influenced by the fact that the inhaler was not used in 2 weeks. After reviewing the entire instruction related to this task, (b) (4) stated it was clear to shake and spray for re-activation and suggested no changes to the instructions (page 112). **2) Failure to completely describe reactivation:** (b) (4) (Healthy Juvenile Inhaler Naïve) stated to shake but did not state to spray (page 133). **(Low literacy)** (b) (4) correctly knew to activate the inhaler and stated that she would shake it before dosing, but she did not state to spray after shaking. In her failure debrief, (b) (4) admitted to skimming the instructions and only reading the first three words of the instruction before giving her answer ("You must shake then test spray into the air one time before dosing"). After reviewing the entire instruction related to this task, (b) (4) stated it was clear to shake and spray for re-activation and suggested no changes to the instructions (page 112).	(b) (4) was confused by the question and didn't focus on the aspect of not using the inhaler. (b) (4) was focused on the inhaler being dirty, which is why they stated to wash the inhaler (page 132). (b) (4) correctly answered that reactivation is necessary and further articulated the need to shake the inhaler. This participant admitted to only skimming that part of the instruction and thus missed the additional task of a test spray (page 133).	The instructions clearly communicate to shake and spray to reactivate (in 2 different sections), with a dedicated section that includes both a bolded, large header, full descriptive test, and illustrations to reinforce the process (page 112). The study demonstrated that participants know to reactivate the inhaler prior to dosing after 2 weeks of no use. The residual risk associated with this error is acceptable and cannot be further minimized. No mitigation proposed.	Based on our discussion with our CMC colleagues, we understand that the new bench study data showed that inhalers dispensed an acceptable dose (i.e., from 2 sprays data) when they were not re-primed for up to 14 days. However, our CMC colleagues finds a more conservative approach of re-priming daily should be considered to minimize the risk for variability in the dose dispensed. The DNDP review team recommends to revise the instructions to shake and spray into the air 1 time "for every inhalation" (b) (4) Based on DNDP review team's recommendations, (b) (4) thus, we have no further recommendations for this task.

3.3 LABELS AND LABELING

Our review of the labels and labeling identified the proposed container label, actuator label, carton labeling, and IFU may be improved editorially for consistency across all labels and labeling pieces. We provide our recommendations in Section 4.1.

In addition, we learned from discussions with the review team:

- Although the inhaler will not clog if not washed, CMC noted that the inhaler may deliver an inconsistent dose in the absence of washing. CMC further noted that the data for beyond 7 days of not washing the inhaler is variable (i.e., 7-20 days in the resubmission study, the mean and standard deviation ranged from 103.3 ± 9.2 % to 118.9 ± 19.5%), which suggests a risk of clinically significant dose inconsistencies potentially leading to superpotent doses. Thus, the conservative approach to wash the inhaler every day after use is preferred. The review team also agreed that washing the inhaler more frequently would be beneficial for consumers (e.g., improves consistent dosing and hygiene reasons) and because consumers may not recall correctly if they used the inhaler during the week in actual use. Thus, the review team recommends to instruct consumers to wash the inhaler after "each day of use" (b) (4)
- Similarly, because consumers may not recall correctly if they have used the inhaler during the past 2 weeks in actual use, and because the suspension can settle and lead to dose variability if it is not shaken and sprayed immediately prior to each dose, the review team also recommends to revise the instructions to shake and spray into the air 1 time "for every inhalation" (b) (4)
- The proposed product website contains a section titled "The New Primatene Mist" that states the original Primatene Mist CFC metered dose inhaler (MDI) and the current HFA MDI contain the same epinephrine active ingredient; however, it does not indicate that the inhalers work differently. The review team concluded that the website should be revised to indicate that the inhalers are different.

We do not object with the review team's conclusion to revise the instructions based on the comments above. Thus, the DNDP review team has requested that we consider these changes in our review and include any recommendations we have for the revised language to minimize the potential for medication error.

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

4 CONCLUSION & RECOMMENDATIONS

We conclude that the HF validation (G4) study results demonstrated that the intended user population can use the proposed product safely and effectively. We also conclude that the proposed container label, actuator label, carton labeling, and IFU may be improved editorially for consistency across all labels and labeling pieces. We also include our recommendations for the revised instructions that the DNDP review team has requested to the labels and labeling. We provide our recommendations in Section 4.1, for Armstrong to implement prior to approval.

4.1 RECOMMENDATIONS FOR ARMSTRONG

To improve the consistency across all labels and labeling pieces, we recommend the following:

A. General Comment
    1. The container label refers to a "consumer information insert". The actuator label refers to "read insert before use". The carton labeling PDP refers to an "insert" and side panel refers to "read the Consumer Information Insert…". (b) (4)
B. Actuator Label
    1. Under the green "Dose" panel, revise (b) (4) to read "1. Shake then spray into the air one time."
    2. Under the blue "Wash" panel, revise (b) (4) to read "Wash After Each Day of Use"
C. Carton Labeling
    1. On the PDP, revise the statement "Suspension: (b) (4) " to read "Suspension: (b) (4)"
    2. Under Directions, revise:
        a. (b) (4)" to read (b) (4)Shake then spray into the air 1 time."
        b. (b) (4) to read "Wait 1 minute. If symptoms not relieved, take a second inhalation by repeating steps (b) (4) above."
        c. "Wash inhaler after (b) (4)" to read "wash inhaler after each day of use."
D. Container Label
    1. Under Directions, revise:
        a. (b) (4) to read "Shake then spray into the air one time before each inhalation."
        b. (b) (4) to "If not relieved, shake then spray into the air one time and take a second inhalation."
E. Primatene Mist Website, section titled, "The New Primatene Mist"

1. After the statement, “The new Primatene Mist is a CFC-free metered dose inhaler (MDI) that uses epinephrine as its active ingredient, the same active ingredient used in the previous Primatene Mist.” include the following statement: “The new inhaler works differently from the old inhaler. Be sure to read the Consumer Information Insert for detailed directions on how to correctly use the new Primatene Mist inhaler.”

F. See Appendix H for our recommendations for the Instructions for Use in tracked changes.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Primatene Mist received on May 7, 2018 from Armstrong Pharmaceuticals, Inc.

Table 2. Relevant Product Information for Primatene Mist	
Initial Approval Date	N/A
Active Ingredient	Epinephrine
Indication	For temporary relief of mild symptoms of intermittent asthma • wheezing • tightness of chest • shortness of breath
Route of Administration	Oral inhalation
Dosage Form	Inhalation Aerosol
Strength	0.125 mg per inhalation

Dose and Frequency	Drug Facts Label (DFL) *Directions*: ***Directions:*** ■ read the Consumer Information Insert for detailed directions on how to use this product. ■ **do not use more than directed.** ■ 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 (New Inhaler):*** Activate new inhaler by shaking then spraying into air 4 separate times. ***Each Time You Dose:*** (b) (4) Remove red cap. (b) (4) (b) (4) Exhale completely, place inhaler in mouth. Inhale deeply while pressing down on top of inhaler, then continue the deep breath. Hold breath as long as possible, exhale. Wait 1 minute. If symptoms not relieved, take a second inhalation. ***After use:*** ■ wait at least **4 hours between doses.** ■ do not use more than **8 inhalations in 24 hours.** ■ wash inhaler after (b) (4) Run water through the mouthpiece for 30 seconds.
How Supplied	Container of 160 inhalations
Storage	Store at room temperature, between 15-25°C (59-77°F)
Container Closure	HFA-134a (hydrofluoroalkane) metered dose inhaler

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 23, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, Primatene Mist. Our search identified two previous reviews: a label, labeling and human factors review[c] and a human factors validation study protocol review,[d] and we confirmed that our previous recommendations were implemented.

[c] Jones, G. Label, Labeling, and Human Factors Review for Primatene Mist NDA 205920. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 DEC 06. RCM No.: 2016-1526.

[d] Jones, G. Human Factors Validation Study Protocol Review for Primatene Mist NDA 205920. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 02. RCM No.: 2017-2312.

APPENDIX C. HUMAN FACTORS STUDY

Link to the human factors validation (G4) study results report:

\\cdsesub1\evsprod\nda205920\0071\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\api-e004-cl-g4\api-e004-cl-g4-report.pdf

Link to the Response to Information Request received on 08/24/2018:

\\cdsesub1\evsprod\nda205920\0075\m1\us\narrative-response.pdf

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On August 23, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Newsletter Community Newsletter Nursing Newsletter
Search Strategy and Terms	Match Exact Word or Phrase: Primatene

D.2 Results

Our search did not retrieve any results.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

On August 23, 2018, we searched FAERS using the criteria in the table below and identified 1 case. We individually reviewed the case, and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[e]

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	Gap Search: October 1, 2016 to August 23, 2018 (from the date of the FAERS search in the previous Primatene Mist Label Labeling Human Factors Review[f] to the current search date)
Product Name:	Primatene Mist
Event:	SMQ *Medication errors* (Narrow)
Country (Derived):	USA

E.2 Results

Our search identified 1 case, which was reported in November 2016. This case was not relevant for this review and was excluded because the errors that the report described (drug ineffective for unapproved indication, expired product administered, product used for unapproved indication) were related to other drug products and unrelated to Primatene Mist. The reporter noted having used Primatene Mist 5 to 6 years ago.

E.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[e] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

[f] Jones, G. Label, Labeling, and Human Factors Review for Primatene Mist NDA 205920. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 DEC 06. RCM No.: 2016-1526.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Primatene Mist labels and labeling submitted by Armstrong received on May 7, 2018.

- Container label (on the container/canister containing the drug product)
- Actuator label (on the mouthpiece)
- Carton labeling
- Instructions for Use

G.2 Label and Labeling Images

Container Label:

(b) (4)

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

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

/s/

GRACE JONES
10/19/2018

DANIELLE M HARRIS on behalf of QUYNHNHU T NGUYEN
10/19/2018

DANIELLE M HARRIS
10/19/2018

Labeling Review for [redacted] (b) (4)

Resubmission #2

SUBMISSION DATES:	June 28, 2016 September 6, 2016 December 2, 2016 May 4, 2018
NDA/SUBMISSION TYPE:	205920/ Class 2 resubmission
ACTIVE INGREDIENTS:	Epinephrine 0.125 mg/inhalation
DOSAGE FORM:	Aerosol, metered
SPONSOR:	Armstrong Pharmaceuticals, Inc. 25 John Road Canton, Massachusetts 02021 Gisela Sharp Senior Manager, Regulatory Affairs (909) 980-9484, ext. 2016
REVIEWER:	Michelle D. Walker, PhD IDS Pharmacologist, DNDP
TEAM LEADER:	Steven Adah, PhD Lead Chemist, DNDP
PROJECT MANAGER:	Tinya Sensie, MHA Regulatory Project Manager, DNDP

I. BACKGROUND

On June 28, 2016, the sponsor submitted a Class 2 resubmission for NDA 205920. This NDA is for [redacted] (b) (4) (epinephrine 125 mcg/inhalation) [redacted] (b) (4) aerosol indicated for temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. This product would replace the Primatene Mist CFC product, which was removed from the market on December 31, 2011 to comply with the Montreal Protocol.

NDA 205920 was originally submitted and received by FDA on July 22, 2013. FDA issued a Complete Response to the sponsor on May 22, 2014 indicating that the NDA would not be approved until the deficiencies were addressed.

On November 29, 2016 the Division of Medication Error Prevention and Analysis (DMEPA) notified the sponsor that proposed proprietary name, Primatene Mist, was approved. Subsequently, the sponsor provided labels, with the exception of the immediate container label, with this proprietary name with the December 2, 2016 submission.

On December 23, 2016 FDA submitted a Complete Response to the sponsor indicating that the NDA would not be approved until the deficiencies were addressed. Specifically, FDA determined that the human factors (HF) 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 OTC setting.

For this submission, the sponsor submitted labeling listed in the table below:

Submitted Labeling	Date(s) submitted
160-spray, 11.7 g outer container label	May 4, 2018
160-spray, 11.7 g immediate container label	May 4, 2018
Actuator label	May 4, 2018
Consumer information insert	May 4, 2018

II. REVIEWER'S COMMENTS

1. (b) (4) 160-spray Outer Container

i. Area outside of the PDP

a. The top panel is revised from the December 2, 2016 label submission. The revised top panel states the following:

See Insert and Side Panels For Special (b) (4) on:
(b) (4)

- Activating your New Inhaler
(b) (4)
- Using Spray Indicator

The statements (b) (4) were removed.

Reviewer's comment: *The top panel directs the consumer to look for special instructions. In order to focus the consumer on those instructions that are unique for this product relative to the CFC version of Primatene Mist, we propose this panel should be revised as follows:*

See Insert and Side Panels for Special (b) (4) on:
- Activating your New Inhaler
- Dosing with your New Inhaler
- Using Spray Indicator

b. The location of the lot number and expiration date are visible on the bottom panel of the outer carton.

Reviewer's comment: *This is acceptable.*

ii. PDP labeling

a. The revised labeling submitted by the sponsor reflected the proprietary name approved by DMEPA, Primatene Mist.

Reviewer's comment*: This is acceptable.*

b. The statement of identity reads, Epinephrine Inhalation Aerosol, 0.125 mg per spray, Bronchodilator.

Reviewer's comment*: This is acceptable. The addition of the strength (per spray) is consistent with current DNDP policy.*

b. The sponsor changed an instruction on the PDP. In the Complete Response letter (12/23/2016), FDA recommended that the statement read, "Suspension: (b) (4) " On the proposed PDP, the statement reads "Suspension: (b) (4)" in white font. (b) (4)

Reviewer's comment*: This is unacceptable. In order for the suspension to be properly primed before administration, per CMC and clinical (see DFL below), there should be at least one shake and spray into the air before each inhalation. This is assuming the drug product has been activated as directed when used for the first time. The sponsor will be directed to revise this statement.*

c. Under the image of the labeled mouthpiece, there is a yellow flag with the following text: NEW FORMULATION: See Important Usage Information on Insert and on Side Panels."

***Reviewer's comment**: This is acceptable. The addition of the flag informs the consumer at the time of purchase that this formulation has changed from the previous Primatene Mist CFC formulation and it is essential to read the detailed instructions on the DFL and CII for correct use of this product. Since this flag contains clinically relevant information for the consumer, the flag can remain on the PDP longer than 6 months. The DNDP clinical team will determine how long the flag should remain on the PDP and will be further discussed in their review.*

iii. Outer Carton Drug Facts Label

a. The following DFL font specifications were submitted:

Drug Facts 9 pt
Drug Facts (continued) 9 pt
Headings 7 pt
Drug Facts body text 7 pt
Bullet: 7 pt
Hairline 0.5 pt
Leading space between lines 7.5 pt
32 characters per inch

***Reviewer's comment**: This is unacceptable. The font specifications do not meet the requirements under 21 CFR 201.66. The sponsor will be informed the following:*

Revise your proposed Drug Facts label type sizes to meet the format requirements specified under 21 CFR 201.66(d), specifically, part 201.66 (d)(2) on letter height and type size and 201.66 (d)(4) on bullet type size (i.e., 5-point).

For your convenience, we provide the following:

a. A link to the electronic Code of Federal Regulations (eCFR). See section 201.66 and scroll down to (d) for format.

https://www.ecfr.gov/cgi-bin/text-idx?SID=9dd6a9a5fd0a03fbd68c1d8a33124145&mc=true&node=se21.4.201_166&rgn=div8

b. Drug Facts label examples of graphic enhancements are found under appendix A to Part 201

https://www.ecfr.gov/cgibin/textidx?SID=f5705478a09bef2a2a091ff561bb8574&mc=true&node=ap21.4.201_1328.a&rgn=div9

In addition, we provide the following two guidances.

c. Guidance for Industry Labeling OTC Human Drug Products

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM150994.pdf

d. Guidance for Industry Labeling OTC Human Drug Products — Questions and Answers

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078792.pdf

b. Under ***Directions:*** some additional subheadings were added with more detailed information on using the inhaler. The additional directions are below:

Before First Use (New Inhaler):
Activate new inhaler by shaking then spraying into air 4 separate times.

Each Time You Dose:
(b) (4) Remove red cap.
(b) (4)
(b) (4) Exhale completely, place inhaler in mouth.
Inhale deeply while pressing down on top of inhaler, then continue the deep breath.
Hold breath as long as possible, exhale.
Wait 1 minute. If symptoms not relieved, take a second inhalation.

After use:
- wait at least **4 hours between doses.**
- do not use more than **8 inhalations in 24 hours.**
- wash inhaler after (b) (4) Run water through the mouthpiece for 30 seconds.

Reviewer's comment*: DNDP discussed with OPQ the need for a priming spray before each inhalation. Based on information provided by OPQ, DNDP has determined that the product should be shaken well and one spray should be released in the air before each inhalation. Additional information can be found in the clinical and OPQ reviews. In order to ensure that the consumer is properly administering the suspension and getting the desired dose of the active ingredient in each spray, the following revisions should be used:*

Each Time You Dose:
(b) (4) Remove red cap.
Shake then spray into the air 1 time.
Exhale completely, place inhaler in mouth.

(b) (4)
Inhale deeply while pressing down on top of inhaler, then continue the deep breath.
Hold breath as long as possible, exhale.
Wait 1 minute. If symptoms (b) (4) not relieved, (b) (4)

Also, CMC determined that in order for the actuator to optimally perform, that the mouthpiece should be washed after each day of use (b) (4) *The "After use:" directions should be edited as follows:*

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 the mouthpiece for 30 seconds.

2. 160-spray Immediate Container Label

a. The revised labeling submitted by the sponsor reflected the proprietary name approved by DMEPA, Primatene Mist.

Reviewer's comment: *This is acceptable.*

b. Under the statement of identity, the statement reads (b) (4)

Reviewer's comment: *This is unacceptable. In order to be consistent with that statement on the PDP, the statement should be written as "For Oral Inhalation Only."*

c. The immediate container label contains reduced labeling information. The label contains active and inactive ingredients, use, some warnings, directions, and storage conditions.

Reviewer's comment: *This is acceptable. The outside carton contains the title, headings, subheadings, and information set forth in paragraphs (c)(1) through (c)(9) of 21 CFR 201.66, the immediate container is not required to carry the full drug facts label per 201.66(c)(5).*

d. The statement of identity reads, Epinephrine Inhalation Aerosol, 0.125 mg per spray, Bronchodilator.

Reviewer's comment*: This is acceptable. As noted above, the inclusion of the strength per spray is per DNDP policy.*

e. In the Active Ingredient section, in parenthesis it states "in each spray."

Reviewer's comment: *This is acceptable.*

f. The statement (b) (4) was removed.

Reviewer's comment: (b) (4)

g. The instruction to spray once in the air before use was not included in the Directions.

Reviewer's comment: *This is not acceptable. As indicated above, under the outer container DFL, after shaking the contents, the inhaler should be sprayed once into the air. The following statements should be written as follows:*

"Adults and children 12 years of age and over: shake then spray into the air one time before each inhalation. 1 to 2 inhalations for each dose. Start with one inhalation, wait at least 1 minute. If not relieved, shake then spray into the air one time and take a second inhalation."

3. Actuator Label

In the Complete Response, FDA recommended that the sponsor change the instructions on the mouthpiece labeling by doing the following:

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

On the proposed label, the sponsor included colored pictograms of the three actions "Activate", "Dose", and "Wash". The instructions are as follows:

Activate, Before First Use Only
1. Shake
2. Test spray into the air

You must repeat both actions 4 times (in red font)

Dose, A dose is 1-2 inhalations
1. (b) (4)
2. Inhale

Wash. (b) (4)
a. Remove the red cap and container.
b. Run water through the mouthpiece for 30 seconds.
c. Shake off excess water.

Reviewer's comment: *This is unacceptable. As previously mentioned, contents of the immediate container must be shaken and sprayed once into the air before administration. Also, CMC determined that the mouthpiece must be washed after each day of use. The instructions should be edited as follows:*

Dose, A dose is 1-2 inhalations
1. Shake then spray into the air one time
2. Inhale

Wash, After Each Day of Use
1. Remove the red cap and container.
2. Run water through the mouthpiece for 30 seconds.
3. Shake off excess water.

4. Consumer Information Insert (CII)

a. The CII was changed from 2 separate pages to one larger fold-out paper.
Reviewer's comment*: This is acceptable.*

b. The asthma alert is not listed on the CII.

Reviewer's comment: *To ensure that consumers have as much access to the asthma alert as possible, it should also be included on the CII. The asthma alert is very important in directing the consumer when it is necessary to seek medical attention during an asthma crisis. The suggested location is directly under the red box containing the indication for Primatene Mist and above the Important Information box. The asthma alert is listed below:*

Asthma alert: Because asthma may be life threatening, see a doctor if you
- ■ are not better in 20 minutes
- ■ get worse
- ■ need more than 8 inhalations in 24 hours
- ■ have more than 2 asthma attacks in a week

These may be signs that your asthma is getting worse.

c. In the **Important Information** box on the upper left side of the CII, the following statements were removed, (b) (4)

Reviewer's comment*: This is acceptable. The team has evaluated the deleted language* (b) (4) *The washing instruction is provided in other sections of the CII.*

d. In the **Important Information** box, there is an instruction which states, (b) (4)

Reviewer's comment: This is unacceptable. As stated above, the spray into the air instruction should be included. The instruction should be as follows: "Shake then spray into the air 1 time before each inhalation."

e. On the third panel, in the **Important to Know** box, spray into the air was not included with the spray instruction for the second step.

Reviewer's comment: This is unacceptable. As stated above, the spray into the air instruction should be included. The instruction should be as follows: "Shake then spray into the air 1 time (b) (4) before each inhalation. See Panel B below."

f. In the **Important to Know** box, there is a statement (b) (4)

Reviewer's comment: *Since FDA is requiring that a priming step be done before each inhalation, this statement is not needed, so it should be deleted.*

g. In the **Important to Know** box, there is an instruction to wash the inhaler (b) (4) (b) (4)

Reviewer's comment: *The instruction should be changed to wash the inhaler after each day of use.*

h. There is a section instructing the consumer (b) (4)

Reviewer's comment: *Since FDA is requiring that a priming step be done before each inhalation, this section is not needed, so it should be deleted.*

i. The instructions are placed under one larger section labeled, "Step-By-Step Instructions." More pictograms are included compared to the last reviewed label.

Reviewer's comment*: This is acceptable.*

j. Under B. Dosing with Your Inhaler, a general statement is written as follows:

(b) (4)

Reviewer's comment: (b) (4) *The statement should be written as follows:*

For every inhalation: Shake then → Spray into the Air → Inhale → Wait

k. For the shaking instruction, title of the section is (b) (4)

Reviewer's comment: *Since it is necessary to shake and spray before taking an inhalation, the title should be "Shake then Spray into the Air."*

l. In section B, under the **Shake** panel, the spray into the air instruction is not included.

Reviewer's comment*: This is unacceptable. The instruction should state, "2. Shake then spray into the air 1 time to mix the medicine (Figure D)." This is required in order for the mouthpiece to be properly primed before administering the drug.*

m. In section B, the statement "Shaking inhaler is critical" was added in red text.

Reviewer's comment*: This is acceptable. But text should be changed to include spraying into the air to read, "Shaking and spraying the inhaler are critical.".*

n. Under the "Wait at least 1 minute section", there is an instruction on what to do if no relief is achieved after 1 minute.

Reviewer's comment*: So that the instruction is more clear to the consumer, it recommended that the instruction be stated as follows: "If symptoms are not relieved after at least 1 minute (Figured G), take a second inhalation by repeating steps 2 to 7 above."*

o. As with other labeling, in section C, **Washing Your Inhaler**, the washing instruction is to wash after (b) (4)

Reviewer's comment: *This is unacceptable.* In the washing instruction, (b) (4) should be changed to day.

5. Website

a. There are images of the mouthpiece and the PDP of the outer container on some of the pages.

Reviewer's comment*: The images will have to be changed once the labeling has been edited.*

b. The text used on the website should be consistent with the language recommended on the outer container, actuator, the Drug Facts labeling for the outer container, and the consumer information insert. So edits should be done, where applicable.

c. The ***Directions*** in the DFL is condensed to four bulleted statements:
   - read the Consumer Information Insert for detailed directions on how to use this product.
   - do not use more than directed.
   - 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.

Reviewer's comment*: This is unacceptable. The* ***Directions*** *in the DFL on the website should mirror the complete DFL on the outer container.*

d. *The videos on page 4 were reviewed.*

Reviewer's comment*: The recommendations for the videos are as follows:*

1. *Parts of the Inhaler video –*
   - *The the labeling in the video must be consistent with the approved labeling.*
2. *Understanding the Spray Indicator video –*
   - *The labeling in the video must be consistent with the approved labeling.*
3. *Activating Your Inhaler video –*
   - *No recommendations*
4. *Dosing with Your Inhaler video –*
   - *At 0:41, the text at the bottom of screen states, "and should be used when you need to take a dose or puff of medication." The statement to be edited to "and should be used when you need to take a dose or* (b) (4) *of medication."*
   - *At 0:52, add "Shake then Spray 1 time" step.*
   - *At 1:32, add "Shake then Spray 1 time" step.*
   - *At 2:08, change washing instruction to "wash at least 30 seconds after each day of use."*
5. *Washing Your Inhaler video-*
   - *At 0:24, change washing instruction to* (b) (4)

6. (b) (4)

- (b) (4)

e. There is a webpage displaying the consumer information insert.

Reviewer's comment: *It should be consistent with the final approval for the consumer information insert.*

f. On page 6, under the heading "The New Primatene MIST," there is a sentence mentioning the previous Primatene Mist product.

Reviewer's comment: *To avoid confusing the consumer that the CFC and HFA Primatene products are the same, the statement should be changed to "The new* (b) (4) *works differently from the old inhaler. Be sure to read the Consumer Information Insert for detailed directions on how to correctly use the new Primatene Mist inhaler."*

g. On page 6, under the heading "Preparing Primatene MIST for the First Time Use", there is an instruction that states, "d. Shake then test spray into the air."

Reviewer's comment: *The numbering should be changed to "c" from "d".*

h. On page 6, there is a heading titled "New Requirements to Shake (b) (4) This is the information under the heading, "Every time you use your inhaler, before you take an inhalation, you must shake (b) (4)

Reviewer's comment: *To be consistent with recommendations of the other labeling, the heading should be edited to "New Requirements to Shake then Spray into the Air 1 Time Before Each Use." The statement below the heading should be edited to "Every time you use your inhaler, before you take an inhalation, you must shake then spray into the air 1 time before each use."*

i. (b) (4) FDA is requiring that a priming step be done before each inhalation.

j. On p. 7, there is a section on washing instructions for the mouthpiece. The instruction says to wash inhaler after (b) (4)

Reviewer's comment: *CMC determined that the mouthpiece must be washed after each day of use. The instructions should be edited as follows, "Wash your inhaler after each day of use."*

III. RECOMMENDATIONS

We currently recommend an Information Request to communicate the following labeling deficiencies to the sponsor:

Required changes to areas outside of the principle display panel (PDP)

1. **The sponsor needs to amend some of the bullets on the top panel so that the instructions are clearer to the consumer. The sponsor should use the text edits below:**

   See Insert and Side Panels for Special (b) (4) on:
   - **Activating your New Inhaler**
   - **Dosing with your New Inhaler**
   - **Using Spray Indicator**

Required changes on the PDP

1. **The suspension statement needs to be changed to "Suspension: (b) (4) "**

Required changes to the Outer Carton Drug Facts Label

1. **Revise your proposed Drug Facts label type sizes to meet the format requirements specified under 21 CFR 201.66(d), specifically, part 201.66 (d)(2) on letter height and type size and 201.66 (d)(4) on bullet type size (i.e., 5-point).**

   For your convenience, we provide the following:

   a. A link to the electronic Code of Federal Regulations (eCFR). See section 201.66 and scroll down to (d) for format. https://www.ecfr.gov/cgi-bin/text-idx?SID=9dd6a9a5fd0a03fbd68c1d8a33124145&mc=true&node=se21.4.201_166&rgn=div8

   b. Drug Facts label examples of graphic enhancements are found under appendix A to Part 201 https://www.ecfr.gov/cgibin/textidx?SID=f5705478a09bef2a2a091ff561bb8574&mc=true&node=ap21.4.201_1328.a&rgn=div9

   In addition, we provide the following two guidances.

   c. Guidance for Industry Labeling OTC Human Drug Products https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM150994.pdf

   d. Guidance for Industry Labeling OTC Human Drug Products — Questions and Answers https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078792.pdf

2. **Under *Directions,* the following revisions should be used:**

Each Time You Dose:

1. **Remove red cap.**
2. **Shake** (b) (4) **then spray into the air 1 time.**
3. **Exhale completely, place inhaler in mouth.**
4. **Inhale deeply while pressing down on top of inhaler, then continue the deep breath.**
5. **Hold breath as long as possible, exhale.**
6. **Wait 1 minute. If symptoms** (b) (4) **not relieved,** (b) (4)

After use:

1. **wait at least 4 hours between doses.**
2. **do not use more than 8 inhalations in 24 hours.**
3. **wash inhaler after each day of use. Run water through the mouthpiece for 30 seconds.**

Required changes to the Immediate Container Label

1. **Under the statement of identity, the statement should be written as "For Oral Inhalation Only."**
2. **Under Directions, the statements should be written as follows: "Adults and children 12 years of age and over: shake then spray into the air one time before each inhalation. 1 to 2 inhalations for each dose. Start with one inhalation, wait at least 1 minute. If not relieved, shake then spray into the air one time and take a second inhalation."**

Required changes to the Actuator Label

1. **The instructions should be edited as follows:**

<u>Dose</u>, A dose is 1-2 inhalations

1. **Shake then spray into the air one time**
2. **Inhale**

<u>Wash</u>, After Each Day of Use

3. **Remove the red cap and container.**
4. **Run water through the mouthpiece for 30 seconds.**
5. **Shake off excess water.**

Required changed to the Consumer Information Insert (CII)

1. **Place the asthma alert directly under the red box containing the indication for Primatene Mist and above the Important Information box. The asthma alert is listed below:**

   Asthma alert: Because asthma may be life threatening, see a doctor if you
   ■ are not better in 20 minutes
   ■ get worse
   ■ need more than 8 inhalations in 24 hours
   ■ have more than 2 asthma attacks in a week
   These may be signs that your asthma is getting worse.

2. **In the Important Information box, the instruction should be stated as follows: "Shake then spray into the air 1 time before each inhalation."**
3. **On the third panel, in the Important to Know box, the instruction should be stated as follows: "Shake then spray into the air 1 time before each inhalation."**
4. **In the Important to Know box, the instruction (b) (4) should be deleted.**
5. **In the Important to Know box, the statement (b) (4) should be deleted.**
6. **In the Important to Know box, the washing instruction should be changed to wash (b) (4) inhaler after each day of use.**
7. **The section instructing the consumer (b) (4) should be deleted.**
8. **Under B. Dosing with Your Inhaler, the statement is written as follows: " For every inhalation: Shake then → Spray into the Air → Inhale → Wait"**
9. **The heading in the (b) (4) box should be changed to "Shake then Spray into the Air."**
10. **In section B, under the Shake panel, a second step should be edited to "2. Shake then spray into the air 1 time to mix the medicine (Figure D)."**
11. **The warning statement should be changed to "Shaking and spraying the inhaler are critical."**
12. **Under the "Wait at least 1 minute section", the instruction should be written as follows: "If symptoms are not relieved after at least 1 minute (Figured G), take a second inhalation by repeating steps 2 to 7 above."**
13. **In section C, Washing Your Inhaler, in the washing instruction (b) (4) should be changed to day.**

Required changes to the website

1. **There are images of the labeling and mouthpiece will have to be changed once the labeling has been edited.**

2. **The text used on the website should be consistent with the language recommended on the outer container, actuator, the Drug Facts labeling for the outer container, and the consumer information insert. So edits should be done, where applicable.**
3. **The Directions in the DFL on the website should mirror the complete DFL on the outer container.**
4. **Videos**
   - **(a) Parts of the Inhaler video – The labeling in the video must be consistent with the approved labeling.**
   - **(b) Understanding the Spray Indicator video –**
     - **The labeling in the video must be consistent with the approved labeling.**
   - **(c) Activating Your Inhaler video –**
     - **No recommendations**
   - **(d) Dosing with Your Inhaler video –**
     - **At 0:41, the text at the bottom of screen states, "and should be used when you need to take a dose or puff of medication." The statement to be edited to "and should be used when you need to take a dose or (b) (4) of medication."**
     - **At 0:52, add "Shake then Spray 1 time" step.**
     - **At 1:32, add "Shake then Spray 1 time" step.**
     - **At 2:08, change washing instruction to "wash at least 30 seconds after each day of use."**
   - **(e) Washing Your Inhaler video-**
     - **At 0:24, change washing instruction to (b) (4)**
   - **(f) (b) (4)**
     - (b) (4)
5. **There is a webpage displaying the consumer information insert *should be consistent with the final approval for the consumer information insert.***
6. **On page 6, under the heading "The New Primatene MIST," *the statement should be changed to "The new (b) (4) works differently from the old inhaler. Be sure to read the Consumer Information Insert for detailed directions on how to correctly use the new Primatene Mist inhaler."***
7. **On page 6, under the heading "Preparing Primatene MIST for the First Time Use", the numbering for the instruction should be changed to "c" from "d".**
8. **On page 6, there is a heading titled (b) (4) The heading should be edited to "New Requirements to Shake then Spray into the Air 1 Time Before Each Use." The statement below the heading**

should be edited to "Every time you use your inhaler, before you take an inhalation, you must shake then spray into the air 1 time before each use."

9. (b) (4)

10. **On p. 7, there is a section on washing instructions for the mouthpiece. The instruction edited to, "Wash your inhaler after each day of use."**

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

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

/s/

MICHELLE D WALKER
10/15/2018

STEVEN A ADAH
10/15/2018

HUMAN FACTORS VALIDATION STUDY PROTOCOL REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 2, 2018
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 205920
Product Type:	Combination Product
Drug Constituent Name and Strength	Primatene Mist (Epinephrine) Inhalation Aerosol, 0.125 mg per inhalation
Device Constituent:	Inhaler
Rx or OTC:	OTC
Applicant/Sponsor Name:	Armstrong Pharmaceuticals, Inc. (Armstrong)
Submission Date:	November 8, 2017 and December 5, 2017
OSE RCM #:	2017-2312
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
DMEPA Deputy Director (Acting):	Danielle Harris, PharmD, BCPS

1. REASON FOR REVIEW

The Division of Nonprescription Drug Products consulted DMEPA to review the proposed human factors validation study protocol submitted under NDA 205920 for Primatene Mist (epinephrine inhalation aerosol). This is a combination product with a proposed inhaler device constituent part that is indicated for the temporary relief of mild symptoms of intermittent asthma in adults and children age 12 and older.

1.1 REGULATORY HISTORY

Primatene Mist (epinephrine) inhalation aerosol was approved on November 8, 1967, under NDA 016126 and originally marketed by Wyeth Consumer Healthcare, as an OTC product indicated for the temporary relief of occasional symptoms of mild asthma. Armstrong was the contract manufacturer of Primatene Mist from 2004 to 2008, and acquired the product from Wyeth on July 8, 2008. Armstrong marketed Primatene Mist until December 31, 2011, when it was withdrawn from distribution due to the phase out of chlorofluorocarbons (CFC) outlined in the Montreal Protocol.

Since then, Armstrong has re-formulated the epinephrine inhalation aerosol using HFA-134a (hydrofluoroalkane) as the propellant. On July 20, 2013, the Applicant submitted the re-formulated epinephrine HFA inhalation aerosol for review under NDA 205920. On May 22, 2014 the application received a Complete Response (CR) letter. On June 28, 2016, the Applicant resubmitted their application. The application received a CR letter on December 23, 2016. The December 23, 2016, CR stated the human factors study (G3) failed to demonstrate that the Primatene Mist user interface supports the safe and effective use of the product by intended users for the proposed OTC use of Primatene Mist. To address the deficiency, the letter recommended the Applicant optimize the user interface and validate the changes to the interface in a human factors study.[1] On November 8, 2017, the Applicant submitted a human factors validation study protocol, the subject of this review.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

[1] The Applicant submitted an End of Review Conference request on February 22, 2017, which the Agency granted a teleconference meeting for March 23, 2017. Then the Applicant submitted a Formal Dispute Resolution request on June 27, 2017, which the Agency denied on September 1, 2017.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA) and FDA/Sponsor Interactions	B
Human Factors Validation Study Protocol	C
Review of Product Sample	D
Information Requests Issued During the Review	E
CDRH Human Factors Consult Review	N/A

3. REVIEW SUMMARY AND DISCUSSION

Our review notes that the Applicant stated the tasks (b) (4) The Applicant asserts that the bench studies, included in this submission, (b) (4) For the dosing task, the Applicant determined that this is a critical task. Because NDA 205920 is currently in CR status, the bench studies will not be reviewed until the NDA resubmission. While the review of the bench data will inform the determination whether the aforementioned tasks will be considered as critical tasks, agreement cannot be reached with the Applicant at this time. Thus, we provide specific recommendations to facilitate the collection of granular HF study data to be submitted as part of the NDA resubmission to ensure adequate data is available for review with the future NDA submission. For example, the Applicant should collect data on whether the participant shook, sprayed, how many times of each, and in which order, and seconds needed to complete the sequence. In addition, the Applicant should collect data on the duration when the participants wash the inhaler as well as the orientation of the inhaler. See recommendations 1 and 2 in section 4.2 below.

In addition, we have identified five areas of the protocol that would require additional information or modification to ensure the methods are appropriate for the HF validation study.

1. Study endpoints are not clearly defined and inconsistent. Page 53 of the proposed protocol states (b) (4)

2. In the simulated use task 3, washing the inhaler, two knowledge probe questions occur before the actual simulated use task. Asking participants knowledge probe questions prior to participants performing the task can induce bias on the user performance data that will be collected during simulated use session.
3. The study script uses leading language and provides descriptive instructions on how to use the product, which is not reflective of real-world use.
4. In Appendix B – Condition Log (page 64), it states at least 15% low literacy, which does not align with previous agency advice to include at least 25% low literacy participants included in the study.[2] In addition, there is a discrepancy in the percentage of low literacy participants because in the Validation Study Methods Study Design (page 37), it states at least 25% of subjects with low literacy would be included.
5. The study script includes observations of the participant during the simulated use tasks 1 through 3; however, it does not include documentation on which user interface (IFU, or container label, etc.) the participant referred to or used during the simulated use tasks.

See recommendations 3-8 in section 4.2 below.

We also evaluated the proposed product user interface (See Appendix D). Our overall assessment finds that based on the available information at the time of this review, we have no recommendations at this time.

4. CONCLUSION & RECOMMENDATIONS

The human factors validation study protocol has areas that required revisions. Please see our recommendations in sections 4.1 and 4.2 below. We advise that the Applicant implements our recommendations prior to commencing their human factors validation study.

4.1 RECOMMENDATIONS FOR THE DIVISION

Our review of the proposed human factors validation study protocol identified several areas of concern where changes or additional information is necessary. We recommend that the protocol be revised to address our concerns and to ensure that the methodology is acceptable. Please see recommendations in Section 4.2 below that should be conveyed to Armstrong Pharmaceuticals, Inc. before they commence their human factors validation study.

4.2 RECOMMENDATIONS FOR ARMSTRONG PHARMACEUTICALS, INC.

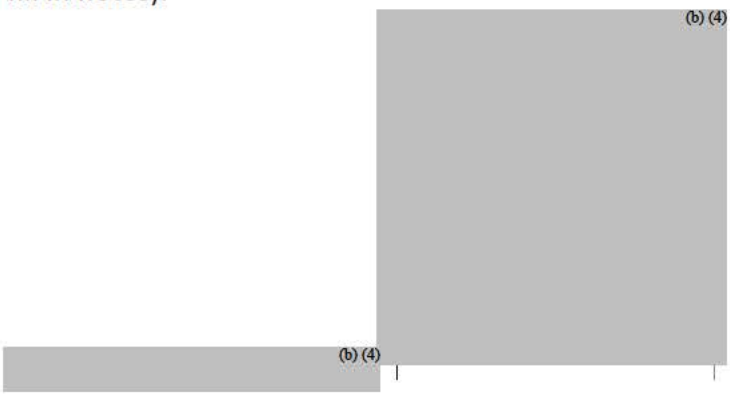
[2] Sensie T. Information Request, General Advice Letter for Primatene Mist NDA 205920 dated 2017 OCT 31. Armstrong Pharmaceuticals Inc.

Our review of your human factors validation study protocol identified several areas of concern. Please address the comments provided below before commencing your human factors (HF) validation study.

We acknowledge your use-related risk analysis and your five bench study reports included in your submission. We also acknowledge that your proposed performance measures and your determination of "minimal acceptable performance" are based on your bench study data. For example, on page 54 of 79 of your HF protocol, the minimal acceptable performance criteria is listed as "the user must rinse water through the mouthpiece (either end for at least 2 seconds)", which is based on your bench study reports. However, your bench study reports will be reviewed after the NDA is resubmitted and the findings from your bench studies will be a review issue. Thus, it is premature to reach agreement on the performance measures proposed in your HF validation study. Therefore, to ensure adequate data is available for review with the future NDA submission, we recommend collection of granular HF study data to be submitted as part of the NDA resubmission. As such, we have recommendations 1 and 2 below to facilitate the collection of HF data that would be necessary to be included in your NDA.

1. For task 1, inhaler activation
    a. Capture the following for all participants in an Excel file for NDA submission to ensure that the data from your study report provides whether the participants shook, sprayed, how many times of each, and in which order, and seconds needed the complete the sequence. For example consider the following headers:
        i. Column 1: record "shake and spray", "shake once, then spray", "did not shake and spray", or "other".
            - If "Other", record what the participant did in a "notes" column.
        ii. Column 2: record number of time(s) the action in column 1 was performed.
            - If "shake once, then spray", then the number recorded in column 2 should indicate the number of times the action was performed.
            - If "did not shake and spray", then the number "0" should be recorded in column 2.
        iii. Column 3: record number of seconds to complete the action in column 1.
            - If "did not shake and spray", then "0" seconds should be recorded in column 3.

iv. Column 4: record "into air", "in mouth", "towards face", "other" (if other, fill in notes).



2. For task 3, washing the inhaler

   a. Capture the following for all participants in an Excel file for NDA submission:

      i. Column 1, removed the container prior to washing: record yes or no.

      ii. Column 2, run water through canister-end opening: record yes or no.

      iii. Column 3, number of seconds for column 2 action: record number of seconds.

      iv. Column 4, run water through mouthpiece-end opening: record yes or no.

      v. Column 5, number of seconds for column 4 action: record number of seconds.

In addition, our review of the proposed HF validation study protocol identified areas for improvement. Please address the following before commencing your HF validation study.

3. Provide task success and failure for Task 1, inhaler activation. Page 53 of the proposed protocol states (b) (4) Revise your study protocol to clearly and consistently define task success and failure.

4. As proposed, (b) (4)

[redacted] (b) (4) We recommend that study participants perform the simulated use task first, and then after performance of the task the moderator may ask the knowledge probe questions to assess further for comprehension.

5. The moderator study script uses leading language, which provides descriptive instructions on how to use the product and is not reflective of real-world use. Revise the moderator script to non-leading language. For example,

    a. For unaided task 1 and 2 on page 70, revise the statement [redacted] (b) (4) to read "You have just removed this product from the carton for the first time. Show me what you would do with this product at this point so that you can use it later when you actually have asthma symptoms."

    b. For unaided task 3 on page 73, revise the statement [redacted] (b) (4) to read "Let's assume you have been using your inhaler for 1 full week, is there something you would do with your inhaler after using it for a week?"

6. We acknowledge your HF validation study methods indicate you intend to recruit at least 25% of participants with low literacy in the study. However, in Appendix B – Condition Log (page 64), you indicate at least 15% low literacy. We recommend you address the discrepancy and ensure that you include at least 25% low literacy participants in your study.

7. We acknowledge that you already plan to document the time that participants spent interacting with the various user interfaces (e.g. the IFU, carton, and inhaler label) during "Study Introduction and Self-Directed Interaction" (page 69 of Study Script). Consider also collecting whether participants referred to the IFU, carton, and/or the inhaler label for each task during the HF study. This information may be useful to determine which aspect of the user interface may be further optimized.

In addition, please note that when you conduct the study and if you observe use related errors and failures, the Agency expects that you apply the human factors engineering process to implement necessary changes to the product user interface. Depending on the nature of changes and the risk, you may need to perform additional human factors validation study to demonstrate the effectiveness of the changes.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Primatene Mist that Armstrong Pharmaceuticals, Inc. submitted on November 8, 2017.

Table 2. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Bronchodilator
Active Ingredient (Drug or Biologic)	Epinephrine
Indication	Temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older
Route of Administration	Oral inhalation
Dosage Form	Aerosol
Strength	0.125 mg per inhalation
Dose and Frequency	Adults and children 12 years of age and over: 1 to 2 inhalations for each dose. Start with one inhalation, wait at least 1 minute. If not relieved (b) (4) Wait at least 4 hours between doses. Do not use more than 8 inhalations in 24 hours. Children under 12 years of age: do not use
How Supplied	Container of 160 inhalations
Storage	Store at room temperature, between 15-25°C (59-77°F)
Container Closure/Device Constituent[3]	The container consists of: 14 mL pharmaceutical aerosol can, (b) (4) The valve consists of: (b) (4) Aluminum Anodized Valve, (b) (4) 50 µL metering (b) (4) (b) (4) The actuator/cap consists of: (b) (4) L shape actuator with a (b) (4) orifice; assemble to a (b) (4) cap. Drawing No. (b) (4) (actuator) (b) (4) (cap) The dose counter consists of: (b) (4) Top Mount Actuation Indicator (Model number (b) (4) Part No. (b) (4)
Intended Users	Consumers
Intended Use Environment	OTC use environment

[3] This information is obtained from the June 28, 2016 submission.

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On December 20, 2017, we searched the L:drive and AIMS using the terms, Primatene, to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified a proprietary name review[4] and a label, labeling and human factors review[5] and we confirmed that the Applicant considered our previous recommendations.

B.2 PREVIOUS FDA/SPONSOR INTERACTIONS

On March 23, 2017, DMEPA participated in a Type A meeting, end of review conference[6], for NDA 205920.

DMEPA provided comments in the General Advice letter for NDA 205920, dated October 31, 2017.[7]

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[4] Jones, G. Proprietary Name Review for Primatene Mist NDA 205920. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 01. RCM No.: 2016-10269700.

[5] Jones, G. Label, Labeling, and Human Factors Review for Primatene Mist NDA 205920. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 DEC 06. RCM No.: 2016-1526.

[6] Sensie, T. Meeting Minutes for Primatene Mist NDA 205920 dated 2017 APR 27. Armstrong Pharmaceuticals Inc.

[7] Sensie T. Information Request, General Advice Letter for Primatene Mist NDA 205920 dated 2017 OCT 31. Armstrong Pharmaceuticals Inc.

APPENDIX C. HUMAN FACTORS VALIDATION STUDY PROTOCOL

The HF study protocol can be accessible in EDR via:
\\cdsesub1\evsprod\nda205920\0067\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\api-e004-cl-g4\api-e004-cl-g4.pdf

APPENDIX D. REVIEW OF PRODUCT SAMPLE

We received product samples of the proposed Primatene Mist (epinephrine) inhalation aerosol, 0.125 mg per inhalation for evaluation. We note the Applicant has made several revisions to the user interface. We have no further recommendations for changes to the interface at this time.

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

Methods:

On December 5, 2017, the Applicant responded to our Information Request (IR) that we issued via email on November 30, 2017 requesting that the Applicant clarify the meaning of the abbreviation, “ibid,” which is used in their Human Factors Validation Study Protocol. The explanation that the Applicant provided was acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GRACE JONES
02/02/2018

CHI-MING TU
02/02/2018

QUYNHNHU T NGUYEN
02/02/2018

QUYNHNHU T NGUYEN on behalf of DANIELLE M HARRIS
02/02/2018

Labeling Review for

[redacted] (b) (4)

Draft Labeling

SUBMISSION DATES:	June 28, 2016 September 6, 2016
NDA/SUBMISSION TYPE:	205920/ Class 2 resubmission
ACTIVE INGREDIENTS:	Epinephrine 0.125 mg/inhalation
DOSAGE FORM:	Aerosol, metered
SPONSOR:	Armstrong Pharmaceuticals, Inc. 25 John Road Canton, Massachusetts 02021 Gisela Sharp Senior Manager/Regulatory Affairs 617-323-7404
REVIEWER:	Michelle D. Walker, PhD IDS Pharmacologist, DNDP
TEAM LEADER:	Steven Adah, PhD Lead Chemist, DNDP
PROJECT MANAGER:	Tinya Sensie, MHA Regulatory Project Manager, DNDP

I. BACKGROUND

On June 28, 2016, the sponsor submitted a Class 2 resubmission for NDA 205920. This NDA is for [redacted] (b) (4) (epinephrine 125 mcg/inhalation) [redacted] (b) (4) aerosol indicated for temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. This product would replace the Primatene Mist CFC product, which was removed from the market on December 31, 2011 to comply with the Montreal Protocol.

NDA 205920 was previously submitted and received by FDA on July 22, 2013. It was not approved by FDA based on deficiencies. FDA submitted a Complete Response to the sponsor on May 22, 2014 indicating that the NDA would not be approved until the deficiencies were addressed.

FDA submitted an information request to the sponsor on August 18, 2016 indicating that the Drug Facts specifications (e.g. bolding, font/type size, headings, barlines, hairlines, bullets, etc.) for the outer container and immediate container labeling should be submitted. On September 6, 2016, the sponsor resubmitted partial annotated specifications for the labeling. Complete annotated specifications have not been submitted at the date of this review.

The sponsor submitted labeling listed in the table below:

Submitted Labeling September 6, 2016*
160-spray, 11.7 g immediate container label
160-spray, 11.7 g outer container label
Consumer information insert**
Product website, www.primatene.com

*No representative SKUs were submitted
**Submitted on June 28, 2016

This review captures the all of the comments generated by the review team which were shared with the sponsor on November 22, 2016. The sponsor's responses will be addressed in addendum 1 to this review.

II. REVIEWER'S COMMENTS

The labeling that the sponsor submitted is reviewed below.

A. (b) (4) 160-spray Outer Container

i. **Label Outside *Drug Facts***

a. **Area outside of the Principle Display Panel (PDP)**

1. The top panel is revised from the April 16, 2014 label submission. The revised top panel states the following:

(b) (4)

Proposed Primatene Mist Top Panel

Reviewer's comment: *This is not acceptable. The following revisions are proposed:*

a. *For the bullet* (b) (4) *the text should be edited to "[bullet]* (b) (4)

b. *The* (b) (4) *bullet should be edited so that the instruction is clearer to the consumer. Suggested text is* (b) (4)

c. *Edit "[bullet]* (b) (4) *to read "[bullet] Using Spray Indicator."*

2. The outer carton label lacks a tamper-evident features statement.

Reviewer's comment: *This is acceptable. According to Compliance Policy Guide Section 450.500 Tamper-Resistant Packaging Requirements for Certain Over-the-Counter Human Drug Products and 21 CFR 211.132. aerosols by design are inherently tamper resistant.*

3. The location of the lot number and expiration date on the outer carton are not identified.

Reviewer's comment: *This is not acceptable. The sponsor must ensure that the lot number and expiration date are visible on the immediate and outer containers, in accordance with 21 CFR 201.17 and 201.18. Though the locations of the lot number and expiration date were specified on the immediate container labeling, the sponsor also has to specify the locations on the outer container.*

b. **PDP labeling**

1. In a letter dated September 19, 2016, the sponsor requested review of a new proposed proprietary name for this product, Primatene Mist.

   Reviewer's comment: *The proprietary name was approved by the Division of Medication Error Prevention and Analysis (DMEPA). The sponsor was notified*

of the approval by letter on November 29, 2016. The sponsor should submit revised labeling with the new trade name.

2. The dosage is stated as 0.125 mg per (b) (4)

   Reviewer's comment: *This is unacceptable.* (b) (4) *should be changed to "spray". The dosage information should be stated as 0.125 mg per spray. "Spray" is preferred over* (b) (4)

3. On the PDP, the statement of identity reads, Epinephrine Inhalation Aerosol, (b) (4)

   Reviewer's comment: *This is unacceptable. The text should be bolded and in white font. The statement of identity should be edited as follows:*

   Epinephrine Inhalation Aerosol

   0.125 mg per spray

   Bronchodilator

3. In the middle of the PDP there is a statement (b) (4)

   Reviewer's comment: *This is unacceptable. In order to be consistent with changes to the priming instruction on the rest of the labels, the instruction should be edited to read "* (b) (4)

4. In the previous labeling review for this NDA, dated May 8, 2014, the sponsor called a banner located on the PDP within the lower 30 percent of the area of the panel a "prominent starburst banner." The banner states (b) (4) See Important Usage Information on Insert and on Side Panels." The sponsor indicated that starburst will remain on the packaging until a sufficient time has elapsed to ensure that previous users are fully informed of the reformulated product and revised usage information.

   Reviewer's comment: *This is unacceptable.* (b) (4) *should be changed to "New Formulation." The statement provides instructions to the consumer to read the carton labeling and consumer information insert for detailed information.*

5. There is a statement that reads (b) (4) on the PDP.

   Reviewer's comment: *This statement should be deleted. This phrase appears on the PDP, DFL, box top, CIL and website. The statement is redundant and distracts the consumer from the essential information on the PDP.*

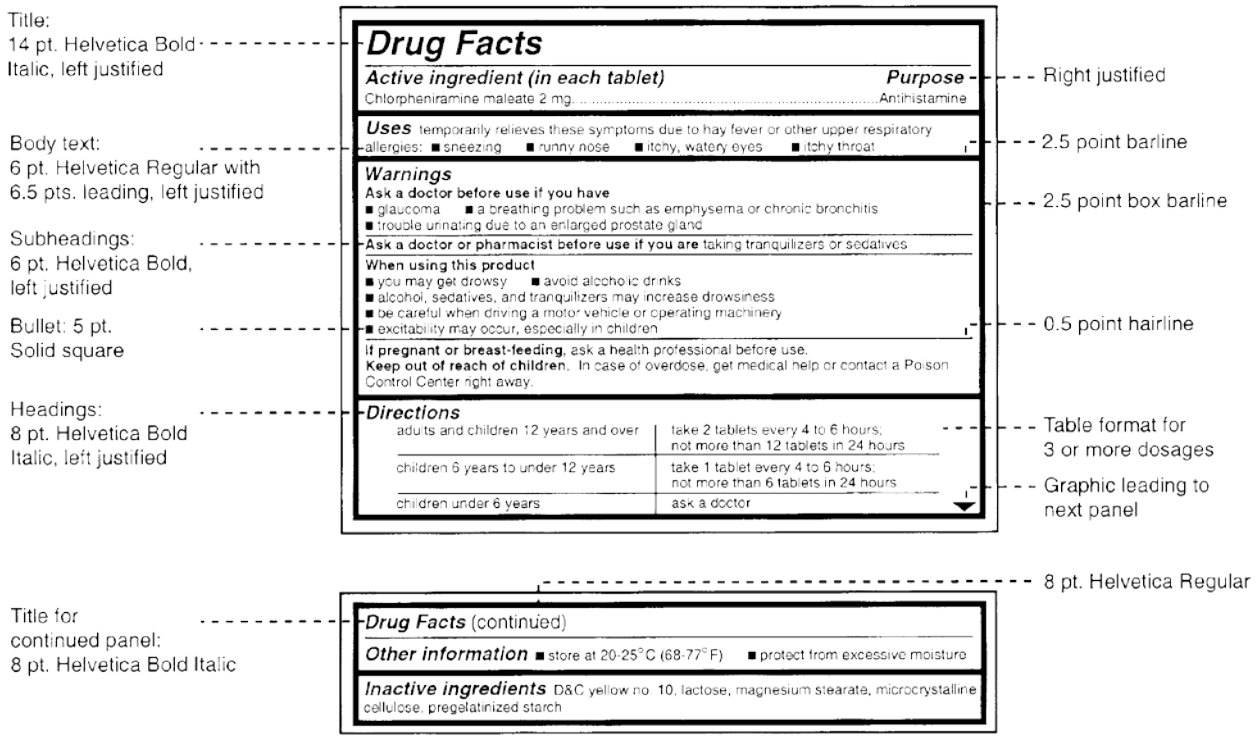
6. The declaration of net quantity statement read [redacted] (b) (4): 11.7 g" and is located on the bottom of the PDP.

   Reviewer's comment: *This is unacceptable. Per 21 CFR 201.62(f), for drugs packed in containers designed to deliver the drugs under pressure, the declaration should state the net quantity of the contents that will be expelled when the instructions for use are followed. The sponsor should move the statement "160 metered sprays" to the lower region of the PDP, above the net weight.*

ii. Outer Carton Drug Facts Label

a. The information in 21 CFR 201.66(c)(1) through (c)(9) should be set off in a box or similar enclosure by the use of a barline. The **Drug Facts** labeling did not include the barlines and hairlines required by 21 CFR 201.66(d)(8). Per 21 CFR 201.66(d)(8), a distinctive horizontal barline extending to each end of the **Drug Facts** box or similar enclosure shall provide separation between each of the headings listed in paragraphs (c)(2) through (c)(9) of 21 CFR 201.66.

   Reviewer's comment: *This is unacceptable. The sponsor should refer to 201 CFR 201.66(d)(8) and 21 CFR Appendix A to Part 201 for formatting information in Drugs Facts. Below is an example of a standard labeling format with the required barlines and hairlines, which is included in 21 CFR Appendix A to Part 201.*



b. An information request from FDA for annotated font specifications was made to the sponsor on August 18, 2016. The sponsor responded in a letter dated September 6, 2016, and included two specifications not previously provided. Complete annotated specifications have not been submitted as of the date of this review. We are aware of the following specifications that have been provided:

Drug Facts 9 pt
Drug Facts (continued) 9 pt
Headings 7 pt
Drug Facts body text 7 pt
Hairline 0.5 pt
Leading space between lines 0.5 pt
32 characters per inch

Reviewer's comment: *This is unacceptable. The sponsor should submit complete Drug Facts font specifications. See 21 CFR 201.66(d) and* ***Guidance for Industry – Labeling OTC Human Drug Products (Small Entity Compliance Guide) May 2009.*** *If the sponsor will be submitting new labeling because of a proprietary name change, complete Drug Facts font specifications should be submitted with the new labeling.*

c. According to 21 CFR 201.66(c), the title, headings, subheadings, and information in 21 CFR 201.66 (c)(1) through (c)(8) should be placed on the Drug Facts labeling in the order listed in the CFR. The headings and subheadings were not placed in the order listed on the submitted Drug Facts labeling.

Reviewer's comment**:** *This is not acceptable. The title, headings and subheadings should be placed in the order listed according to 21 CFR 201.66(c)(1) through (c)(8).*

d. The Active Ingredient heading, in parenthesis, states (b) (4)

Reviewer's comment: *This is not acceptable. The statement should read "in each spray." "Spray" is preferable over* (b) (4)

e. According to 21 CFR 341.76(c)(6)(D), corresponding bullets for the asthma alert for products containing epinephrine should state:

- "are not better in 20 minutes"
- "gets worse"

- **"**need more than 12 inhalations- in 24 hours"
- "use more than 9 inhalations in 24 hours for 3 or more days a week"
- "have more than 2 asthma attacks in a week"

In the submitted Drug Facts labeling, the warning was stated as follows,

- "are not better in 20 minutes"
- "gets worse"
- "need more than 8 inhalations in 24 hours"
- "have more than 2 asthma attacks in a week"

Reviewer's comment*: This is acceptable. The clinical reviewers found the sponsor's proposed changes to the asthma alert language to be acceptable.*

f. There is a bullet in front of the asthma alert statement. According to 21 CFR 341.76(c)(6), there is no bullet before the term "**Asthma alert:"**

Reviewer's comment*: This is unacceptable. The bullet should be removed.*

g. Under the asthma alert, there is a bullet in front of the statement "These may be signs that your asthma is getting worse." There is also no period at the end of the statement. According to 21 CFR 341.76(c)(6)(F), there is a period at the end of and no bullet before this statement.

Reviewer's comment*: This is unacceptable. The bullet should be removed and period should be placed at the end of the statement.*

h. Under ***Warnings***, the bullet for the route of administration, (b) (4) is below the asthma alert.

Reviewer's comment*: This is unacceptable. The sponsor should place the route of administration, in bold type, directly under the* ***Warnings*** *heading without a bullet.* (b) (4) *The warning should read "For oral inhalation only."*

i. Under the **Do not use** subheading, this is no period at the end of the MAOI statement. Per 21 CFR 341.76(c)(ii), there is a period at the end of the statement.

Reviewer's comment*: This is unacceptable. A period should be placed at the end of the statement.*

j. Under the [redacted] (b) (4) subheading, the last bullet states "a psychiatric or emotional condition."

Reviewer's comment: *The clinical reviewer recommended that the sponsor delete this statement. This warning is also under the* ***Ask a doctor or pharmacist before use if you are*** *subheading, so this condition is addressed elsewhere on the label.*

k. Under the **When using this product** subheading, periods are not placed at the end of the following statements,

- **your blood pressure or heart rate may go. This could increase your risk of heart attack or stroke, which may cause death**
- **your risk of heart attack or stroke increases if you**
  - **have a history of high blood pressure or heart disease**
  - **take this product more frequently or take more than the recommended dose**
- avoid foods or beverages that contain caffeine
- avoid dietary supplements containing ingredients reported or claimed to have a stimulant effect

Reviewer's comment*: This is unacceptable. A period should be placed at the end of the following statements, as is required per 21 CFR 341.76(4)(i) through (iv):*

- **your blood pressure or heart rate may go up. This could increase your risk of heart attack or stroke, which may cause death.**
- **your risk of heart attack or stroke increases if you:**
  - **have a history of high blood pressure or heart disease**
  - **take this product more frequently or take more than the recommended dose.**
- avoid foods or beverages that contain caffeine.
- avoid dietary supplements containing ingredients reported or claimed to have a stimulant effect.

l. At the end of the "**When using this product"** statement there is no a colon.

Reviewer's comment*: This is unacceptable. A colon should be placed at the end of* ***When using this product****, as is required per 21 CFR 341.76(4).*

m. Under the **When using this product** subheading, a colon is not placed at the end of the "**your risk of heart attack or stroke increases if you**" statement.

Reviewer's comment*: This is unacceptable. A colon should be placed at the end of "**your risk of heart attack or stroke increases if you**" as is required per 21 CFR 341.76(4)(ii).*

n. There are additional warning statements that are placed after the statements under the **When using this product** subheading on the submitted labeling. The statements are as follows:

i.

- do not puncture or incinerate. Contents under pressure
- do not store near open flame or heat above 120°F (49°C). May cause bursting.

Reviewer's comment: *This is unacceptable. Per 21 CFR 369.21(DRUGS IN DISPENSERS PRESSURIZED BY GASEOUS PROPELLANTS.) the content of the warning should be stated as below. The formatting of the statement is suggested below.*

- avoid spraying in eyes.
- contents under pressure. Do not puncture or incinerate.
- do not store near open flame or heat above 120°F (49°C). May cause bursting.

ii. (b) (4)

Reviewer's comment: *This is unacceptable.* (b) (4)

o. Statements under **Stop use and ask doctor if** follow 21 CFR 341.76(c)(7), with the exception of 21 CFR 341.76(c)(7)(iv). On the submitted labeling, instead of seizure, the plural form was written and there was no period at the end of the sentence.

Reviewer's comment: *This is unacceptable. Per 21 CFR 341.76(c)(7)(iv), the last bullet should be written as "you have tremors, nervousness, and seizure."*

p. Under ***Directions***, the second bulleted statement is "[bullet] do not use more than directed."

Reviewer's comment: *This is unacceptable. Per 21 CFR 341.76(d)(1)(i), the statement "[bullet] do not* (b) (4) *more than directed" should be in bold type and appear as first bulleted statement under "Directions". Per 21 CFR 201.66(d)(4), the first bulleted statement should be separated from an appropriate heading or subheading by at least two square "ems", two squares of the size of the letter "M".*

q. Under ***Directions*** there is no statement directing the consumer to read the Consumer information insert.

Reviewer's comment*: This is unacceptable. There should be a statement instructing the consumer to read the consumer information insert for detailed information on using the product. Suggested text is "[bullet] read in the Consumer information insert for detailed directions on how to use this product." This statement should be under the* ***do not use more than directed*** *statement.*

r. Under ***Directions***, the sponsor provided (b) (4)

Reviewer's comment: *This is unacceptable. The* (b) (4) (b) (4) *should be deleted.* (b) (4)

s. Under ***Directions***, the sponsor included additional bulleted statements that were not required in the CFR.

Reviewer's comment*: This is acceptable.* This information is beneficial to the consumer's use of this product.

t. (b) (4)
.

Reviewer's comment*: This is unacceptable.* (b) (4)

u. The sponsor did not include directions to clean the mouthpiece with water after use.

Reviewer's comment: *This is unacceptable. The statement "* (b) (4) *should be included above the "[bullet] children under 12 years of age: do not use; it is not known if the drug works or is safe in children under 12" section to instruct the consumer to clean the mouthpiece daily following use.* At the end of each of the statements under the "[bullet] adults and children 12 years of age an over" section, there were no periods.

Reviewer's comment: *This is unacceptable. There should be a period at the end of each statement in this section.*

v. The heading (b) (4) is incorrectly labeled.

Reviewer's comment: *This is unacceptable. Per 21 CFR 201.66(c)(7), this heading should be labeled* ***Other Information****.*

w. Under the ***Other information*** heading there is a statement which reads (b) (4)

Reviewer's comment: *This statement should be edited to instruct the consumer on the importance on keeping the outer container labeling and the consumer information insert for detailed information on proper use of the product. Suggested text is "[bullet] keep this label and enclosed materials. They contain important additional information."*

x. CMC confirmed that the ingredient profile in the **Inactive ingredients** section is correct and it follows 21 CFR 201.66(c)(8).

Reviewer's comment*: This is acceptable.*

y. The information in the **Questions or comments?** section follows 21 CFR 201.66(c)(9).

Reviewer's comment*: This is acceptable.*

z. There is an instruction on the bottom of two of panels in enlarged font. It states the following:

(b) (4)

Reviewer's comment: *This is unacceptable. The priming instruction appears on the PDP, Drug Facts labeling, top panel of the outer container, consumer information insert, and on the website. It is redundant to have in two locations at the bottom the Drug Facts labeling panels. Both statements should be deleted.*

B. (b) (4) 160-spray Immediate Container

1. The immediate container label contains reduced labeling information. The label contains active and inactive ingredients, use, some warnings, directions, and storage conditions.

   Reviewer's comment: *This is acceptable. The outside carton contains the title, headings, subheadings, and information set forth in paragraphs (c)(1) through (c)(8) of 21 CFR 201.66, the immediate container is not required to carry the full drug fact label per 201.66(c)(5).*

2. The statement of identity reads, Epinephrine Inhalation Aerosol, (b) (4)

   Reviewer's comment*: This is unacceptable. The statement of identity should be edited as follows:*

   Epinephrine Inhalation Aerosol
   0.125 mg per spray
   Bronchodilator

3. In the Active Ingredient section, in parenthesis in states (b) (4)

   Reviewer's comment: *This is not acceptable. The statement should read "in each spray." "Spray" is preferable over* (b) (4)

4. The statement (b) (4) is on the label.

   Reviewer's comment: *This is unacceptable.* (b) (4)

5. The sponsor did not include directions to clean the mouthpiece with water after use.

   Reviewer's comment: *This is unacceptable. The statement "* (b) (4) *should be included under the* ***Directions*** *heading*

6. There is a warning to (b) (4)

   Reviewer's comment*: This is unacceptable. It is recommended that the sponsor* (b) (4)

C. Consumer Information Insert

(b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

D. Website

1. There are images of the PDP of the outer container on some of the pages.

   Reviewer's comment*: The image will have to be changed once the PDP has been edited.*

2. The text used on the website should be consistent with the language recommended on the PDP, the Drug Facts labeling for the outer container, and the consumer information insert. So edits should be done, where applicable.

III. RECOMMENDATIONS

We currently recommend an Information Request to communicate the following labeling deficiencies to the sponsor:

General

1. On October 31, 2016, an information request (IR) was sent to the sponsor requesting clarification on the (b) (4) statement. It was placed on different areas of the PDP, outer container Drug Facts, the consumer information insert, and on the website. On the consumer information insert, under the (b) (4) section, there was a statement which read (b) (4) FDA requested clarification on the differing language from the sponsor.

   On November 2, 2016, the sponsor responded to the IR indicating that while the statements are worded differently, they do not contradict each other. The sponsor said that the shorter statement was on the outer carton due to space limitations. FDA disagrees, and believes that the statements are different. It is not clear on the outer container statement as to what (b) (4) pertains. (b) (4)

   Also, the consumer information insert has a heading that reads (b) (4) This statement needs clarification. On the Drug Facts label, (b) (4)

   The sponsor needs to be consistent in describing a (b) (4) and revising the priming instruction so that it is clear that a spray is done before each inhalation. (b) (4) which could be up to 2 inhalations.

Outside Container

Required changes to areas outside of the principle display panel (PDP)

1. The sponsor needs to amend some of the bullets on the top panel so that the instructions are clearer to the consumer. The sponsor should use the text edits proposed below:

   a. *For the bullet on priming, the text should be edited to "[bullet]* (b) (4) *"*

b. *The* (b) (4) *bullet should be edited so that the instruction is clearer to the consumer. Suggested text is* (b) (4)

c. *Edit "[bullet]* (b) (4) *to read "[bullet] Using Spray Indicator."*

2. The sponsor must ensure that the lot number and expiration date are visible on the immediate and outer containers, in accordance with 21 CFR 201.17 and 201.18.

Required changes on the PDP

1. The sponsor should submit revised labeling with the new trade name, Primatene Mist.
2. The dosage is stated as 0.125 mg per (b) (4) (b) (4) should be changed to "spray". Spray" is preferred over (b) On the PDP, the statement of identity reads, Epinephrine Inhalation Aerosol, (b) (4) The text should be white font and bolded. The statement of identity should be edited as follows:

   Epinephrine Inhalation Aerosol

   0.125 mg per spray

   Bronchodilator

3. In the middle of the PDP there is a statement In order to be consistent with changes to the priming instruction on the other labels, the instruction should be edited to read (b) (4)
4. The sponsor should move the statement "160 metered sprays" to the lower region of the PDP, above the net weight declaration.

Recommended changes to the PDP

1. In the starburst banner, the sponsor should change the term (b) (4) to "New Formulation."
2. The statement (b) (4) should be deleted.

Required changes on the outer container Drug Facts label

1. The **Drug Facts** labeling did not include the barlines and hairlines required by 21 CFR 201.66(d)(8). The sponsor should refer to 201 CFR 201.66(d)(8) and 21 CFR Appendix

A to Part 201 for formatting information in **Drugs Facts**. An example of a standard labeling format with the required barlines and hairlines can be seen in 21 CFR Appendix A to Part 201.

2. The sponsor should submit complete **Drug Facts** font specifications. See 21 CFR 201.66(d) and **Guidance for Industry – Labeling OTC Human Drug Products (Small Entity Compliance Guide) May 2009**. When the sponsor submits new labeling because of a proprietary name change, complete **Drug Facts** font specifications should be submitted.

3. The headings and subheadings on the **Drugs Facts** labeling were not placed in the order listed in 21 CFR 201.66(c)(1) through (c)(8). The sponsor must place the title, headings and subheadings in the order listed in 21 CFR 201.66(c)(1) through (c)(8).

4. In the Active Ingredient heading, in parenthesis in states (b) (4) The statement should be edited to "in each spray."

5. Under **Warnings,** the bullet for the route of administration, (b) (4) the sponsor should place the route of administration, in bold type, directly under the **Warnings** heading without a bullet. (b) (4) the statement to read "For oral inhalation only."

6. The bullet in front of the asthma alert statement should be removed. According to 21 CFR 341.76(c)(6), there is no bullet before the term "Asthma alert:"

7. Under the asthma alert, the bullet in front of the statement "These may be signs that your asthma is getting worse" Should be removed. There should be a period at the end of the statement per 21 CFR 341.76(c)(6)(F).

8. Under the **Do not use** subheading, a period should be placed at the end of the MAOI statement per 21 CFR 341.76(c)(ii).

9. Under the **When using this product** subheading, a period should be placed at the end of the following statements, as is required per 21 CFR 341.76(4)(i) through (iv):
    - **your blood pressure or heart rate may go up. This could increase your risk of heart attack or stroke, which may cause death.**
    - **your risk of heart attack or stroke increases if you:**
        - **have a history of high blood pressure or heart disease**
        - **take this product more frequently or take more than the recommended dose.**
    - avoid foods or beverages that contain caffeine.
    - avoid dietary supplements containing ingredients reported or claimed to have a stimulant effect.

10. A colon should be placed at the end of **When using this product**, as is required per 21 CFR 341.76(4).
11. Under the **When using this product** subheading, a colon should be placed at the end of "**your risk of heart attack or stroke increases if you**" as is required per 21 CFR 341.76(4)(ii).
12. For the warning statements below, per 21 CFR 369.21(DRUGS IN DISPENSERS PRESSURIZED BY GASEOUS PROPELLANTS.) the content of the warning should be stated as below. The formatting of the statement is suggested.
    - avoid spraying in eyes.
    - contents under pressure. Do not puncture or incinerate.
    - do not store at temperature above 120°F (49°C).
13. (b) (4)
14. The last bullet under **Stop use and ask doctor if** per 21 CFR 341.76(c)(7)(iv) should be written as "you have tremors, nervousness, and seizure." The sponsor should change to the word "seizures" to "seizure" and place a period at the end of the sentence.
15. Under **Directions**, per 21 CFR 341.76(d)(1)(i), the statement "[bullet] do not (b) (4) more than directed" should be in bold type and appear as first bulleted statement under "Directions". Per 21 CFR 201.66(d)(4), the first bulleted statement should be separated from an appropriate heading or subheading by at least two square "ems", two squares of the size of the letter "M".
16. Under **Directions**, the statement "[bullet] do not use more than directed" should as the first bulleted statement.
17. Under **Directions,** (b) (4) The text should be "[bullet] (b) (4)" which is the text suggested (b) (4) instruction for all of the labeling.
18. Under **Directions**, the sponsor did not include directions to clean the mouthpiece with water after use. It is recommended that a statement be included under **Directions** to instruct the consumer to clean the mouthpiece daily following use. Suggested text is (b) (4)
19. The heading (b) (4) is incorrectly labeled. Per 21 CFR 201.66(c)(7), this heading should be labeled **Other Information**.

Recommended changes to the outer container Drug Facts label

1. In order to ensure that the consumer is using the product in the most effective manner, it is recommended that the language used for the [redacted] instruction in the patient information insert mirror what is on the **Drug Facts** labeling. The instruction in the patient information insert says to [redacted] The instruction on the **Drug Facts** label should be the same as that in the patient information insert

2. It is recommended that the sponsor delete the statement "a psychiatric or emotional condition" under the [redacted] section. This warning is also under **the Ask a doctor or pharmacist before use if you are** subheading, so this condition is addressed elsewhere on the label.

3. Under **Directions** there is no statement directing the consumer to read the Consumer information insert. The sponsor should include a statement instructing the consumer to read the consumer information insert for detailed information on using the product. Suggested text is "[bullet] read in the Consumer information insert for detailed directions on how to use this product." This statement should be under the **do not use more than directed** statement.

4. It is recommended that a statement be included above the "[bullet] children under 12 years of age: do not use; it is not known if the drug works or is safe in children under 12" section to instruct the consumer to clean the mouthpiece daily following use. Suggested text is [redacted]

5. Under the Other information heading the [redacted] statement should be edited to instruct the consumer on the importance on keeping the outer container labeling and the consumer information insert for detailed information on proper use of the product. Suggested text is "[bullet] keep this label and enclosed materials. They contain important additional information."

6. A [redacted] is on the bottom of two of panels in enlarged font. The [redacted] appears on the PDP, Drug Facts labeling, top panel of the outer container, consumer information insert, and on the website. It is redundant to have in two locations at the bottom the Drug Facts labeling panels. Both statements should be deleted.

Immediate container

Required changes to the immediate container label

1. [redacted]

(b) (4)

2. The statement of identity reads, Epinephrine Inhalation Aerosol (b) (4) The text should be black font and bolded. The statement of identity should be edited as follows:

   Epinephrine Inhalation Aerosol
   0.125 mg per spray
   Bronchodilator

3. In the Active Ingredient heading, in parenthesis in states (b) (4) The statement should be edited to "in each spray."

4. The statement (b) (4) should be included under the **Directions** heading.

Recommended changes to the immediate container label

1. There is a Warning statement to (b) (4)

Consumer Information Insert (CII)

Required changes to the CII

1. The consumer information insert was reviewed. The text used in the consumer information insert should be consistent with the edits recommended on the Drug Facts labeling for the outer container. So edits should be done, where applicable, for consistency.

Recommended changes to the CII

The following changes are recommended in order to help the consumer to better understand how to properly administer and take care of the inhaler.

(b) (4)

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(b) (4)

Website

Required changes to the website

1. The image of the outer carton PDP on the pages should be updated once the PDP has been edited.

2. The text used on the website should be consistent with the language recommended on the PDP, the Drug Facts labeling for the outer container, and the consumer information insert. So edits should be done, where applicable.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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/s/

MICHELLE D WALKER
12/22/2016

STEVEN A ADAH
12/22/2016

Labeling Review Addendum-1 for [redacted] (b) (4)

Draft Labeling

SUBMISSION DATES:	June 28, 2016 September 6, 2016 December 2, 2016
NDA/SUBMISSION TYPE:	205920/ Class 2 resubmission
ACTIVE INGREDIENTS:	Epinephrine 0.125 mg/inhalation
DOSAGE FORM:	Aerosol, metered
SPONSOR:	Armstrong Pharmaceuticals, Inc. 25 John Road Canton, Massachusetts 02021 Gisela Sharp Senior Manager/Regulatory Affairs 617-323-7404
REVIEWER:	Michelle D. Walker, PhD IDS Pharmacologist, DNDP
TEAM LEADER:	Steven Adah, PhD Lead Chemist, DNDP
PROJECT MANAGER:	Tinya Sensie, MHA Regulatory Project Manager, DNDP

I. BACKGROUND

On June 28, 2016, the sponsor submitted a Class 2 resubmission for NDA 205920. This NDA is for [redacted] (b) (4) (epinephrine 125 mcg/inhalation) [redacted] (b) (4) aerosol indicated for temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. This product would replace the Primatene Mist CFC product, which was removed from the market on December 31, 2011 to comply with the Montreal Protocol.

NDA 205920 was previously submitted and received by FDA on July 22, 2013. It was not approved by FDA based on deficiencies. FDA submitted a Complete Response to the sponsor on

May 22, 2014 indicating that the NDA would not be approved until the deficiencies were addressed.

FDA submitted an information request to the sponsor on August 18, 2016 indicating that the Drug Facts specifications (e.g. bolding, font/type size, headings, barlines, hairlines, bullets, etc.) for the outer container and immediate container labeling should be submitted. On September 6, 2016, the sponsor resubmitted partial annotated specifications for the labeling. Complete annotated specifications have not been submitted at the date of this review. This information request and the sponsor's submission were summarized in the December 20, 2016 draft labeling review.

On November 29, 2016 the Division of Medication Error Prevention and Analysis (DMEPA) notified the sponsor that proposed proprietary name, Primatene Mist, was approved. Subsequently, the sponsor provided labels, with the exception of the immediate container label, with this proprietary name with the December 2, 2016 submission.

Another information request was issued on November 22, 2016, via email. The review team edited and inserted comments on the outer container principle display panel (PDP) and Drug Facts label (DFL), consumer information insert and the website. The changes and comments were submitted to the sponsor in the information request. The sponsor responded the information request with the December 2, 2016 submission.

The sponsor submitted labeling listed in the table below:

Submitted Labeling	Date(s) submitted
160-spray, 11.7 g outer container label	September 6, 2016 and December 2, 2016
160-spray, 11.7 g immediate container label	September 6, 2016
Consumer information insert**	December 2, 2016
Product website, www.primatene.com	December 2, 2016

II. REVIEWER'S COMMENTS

A. (b) (4) 160-spray Outer Container

i. Area outside of the PDP

a. The location of the lot number and expiration date on the outer container has not been identified.

Reviewer's comment: *This is not acceptable. The sponsor must ensure that the lot number and expiration date are visible on the immediate and outer containers, in accordance with 21 CFR 201.17 and 201.18. Though the locations of the lot number and expiration date were specified on the immediate container labeling, the sponsor also has to specify the locations on the outer container.*

ii. PDP labeling

1. The information in 21 CFR 201.66(c)(1) through (c)(9) should be set off in a box or similar enclosure by the use of a barline. The Drug Facts labeling did not include the barlines and hairlines required by 21 CFR 201.66(d)(8). Per 21 CFR 201.66(d)(8), a distinctive horizontal barline extending to each end of the Drug Facts box or similar enclosure shall provide separation between each of the headings listed in paragraphs (c)(2) through (c)(9) of 21 CFR 201.66.

   Reviewer's comment: *This is unacceptable. The sponsor should refer to 201 CFR 201.66(d)(8) and 21 CFR Appendix A to Part 201 for formatting information in Drugs Facts. Below is an example of a standard labeling format with the required barlines and hairlines, which is included in 21 CFR Appendix A to Part 201.*

2. An information request from FDA for annotated font specifications was made to the sponsor on August 18, 2016. The sponsor responded in a letter dated September 6, 2016, and included two specifications not previously provided. Complete annotated specifications have not been submitted as of the date of this review. We are aware of the following specifications that have been provided:

   Drug Facts 9 pt
   Drug Facts (continued) 9 pt
   Headings 7 pt
   Drug Facts body text 7 pt
   Hairline 0.5 pt
   Leading space between lines 0.5 pt
   32 characters per inch

   Reviewer's comment: *This is unacceptable. The sponsor should submit complete Drug Facts font specifications. See 21 CFR 201.66(d) and Guidance for Industry – Labeling OTC Human Drug Products (Small Entity Compliance Guide) May 2009.*

3. The revised labeling submitted by the sponsor reflected the proprietary name approved by DMEPA, Primatene Mist.

   Reviewer's comment*: This is acceptable.*

4. In the November 22, 2016 information request, FDA had edited the statement of identity to read:

Epinephrine Inhalation Aerosol
0.125 mg per spray
Bronchodilator

The labeling resubmitted on December 2, 2016 did not reflect FDA's edit. The statement of identity was written as:

Epinephrine Inhalation Aerosol
(b) (4)

Reviewer's comment: (b) (4) The statement of identity should be written as originally edited by the review team in the November 22, 2016 information request,

Epinephrine Inhalation Aerosol
0.125 mg per spray
Bronchodilator

The text should be in bold type and in white font, so that the text can easily be seen on the PDP since the background is a dark brown.

5. The sponsor inserted the statement "For Oral Inhalation Only" to the PDP.

   Reviewer's comment: This is acceptable. This was the statement drafted by FDA on the DFL in the information request submitted to the sponsor on November 22, 2016.

6. (b) (4)

   Reviewer's comment: (b) (4) the sponsor should place "Suspension", with a colon, before the (b) (4) statement on the PDP. It should be written as follows:

   Suspension:
   (b) (4)

iii. Outer Carton Drug Facts Label

a. Under the asthma alert, there is a bullet in front of the statement "These may be signs that your asthma is getting worse." There is also no period at the end of the statement. According to 21 CFR 341.76(c)(6)(F), there is a period at the end of and no bullet before this statement.

Reviewer's comment: *This is unacceptable. The bullet should be removed and period should be placed at the end of the statement.*

b. Under ***Directions*** the sponsor included directions to clean the mouthpiece with water after use. But the phrase "for 30 seconds" was not in the direction.

Reviewer's comment: *This is unacceptable. The statement should be written on the DFL as* (b) (4)
This is the statement written the CII, so for consistency the same wording should be used in the DFL, CII, and the website.

B. (b) (4) **160-spray Immediate Container**

1. The proposed proprietary name, Primatene Mist, was approved by the Division of Medication Error Prevention and Analysis (DMEPA). The sponsor was notified of the approval by letter on November 29, 2016. The sponsor did not submit revised labeling for the immediate container with the new trade name, Primatene Mist.

   Reviewer's comment: *This is unacceptable. The sponsor must submit revised labeling for the immediate container with the new trade name.*

2. The immediate container label contains reduced labeling information. The label contains active and inactive ingredients, use, some warnings, directions, and storage conditions.

   Reviewer's comment: *This is acceptable. The outside carton contains the title, headings, subheadings, and information set forth in paragraphs (c)(1) through (c)(8) of 21 CFR 201.66, the immediate container is not required to carry the full drug fact label per 201.66(c)(5).*

3. The statement of identity reads, Epinephrine Inhalation Aerosol. (b) (4)

   Reviewer's comment: *This is unacceptable. The statement of identity should be edited as follows:*

   Epinephrine Inhalation Aerosol
   0.125 mg per spray
   Bronchodilator

4. In the Active Ingredient section, in parenthesis in states (b) (4)

   Reviewer's comment: *This is not acceptable. The statement should read "in each spray." "Spray" is preferable over* (b) (4)

5. The statement [redacted] is on the label.

   Reviewer's comment: *This is unacceptable.* [redacted]

6. The sponsor did not include directions to clean the mouthpiece with water after use.

   Reviewer's comment: *This is unacceptable. The statement* [redacted] *should be included under the* ***Directions*** *heading*

7. There is a warning to [redacted]

   Reviewer's comment*: This is unacceptable. It is recommended that the sponsor* [redacted]

C. Consumer Information Insert

a. Under section B. [redacted]

b. Under section C. [redacted]

   Reviewer's comment: *This is unacceptable. So that the statement will be reflect the wording used throughout the CII and other labeling, the statement should be changed to* [redacted] *for consistency.*

D. Website

a. On the first webpage for the website, [redacted] was added to the statement of identity.

   Reviewer's comment: *This is unacceptable. See comment above for an explanation for the statement of identity requirements.*

c. On the DFL page, under the asthma alert, there is a bullet in front of the statement "These may be signs that your asthma is getting worse." There is also no period at the end of the statement.

Reviewer's comment: *This is unacceptable. According to 21 CFR 341.76(c)(6)(F), there is a period at the end of and no bullet before this statement. Since this the requirement for the DFL, the same formatting should be reflected here since the DFL on the carton are the same that on the DFL webpage. The bullet should be removed and period should be placed at the end of the statement.*

d. Under ***Directions*** the sponsor included directions to clean the mouthpiece with water after use. But the phrase "for 30 seconds" was not in the direction.

Reviewer's comment: *This is unacceptable. The statement should be written on the DFL as* (b) (4) *This is the statement written the CII, so for consistency the same wording should be used in the DFL, CII, and the website.*

III. RECOMMENDATIONS

Required changes to areas outside of the principle display panel (PDP)

1. The sponsor must ensure that the lot number and expiration date are visible on the immediate and outer containers, in accordance with 21 CFR 201.17 and 201.18.

Required changes to the PDP

1. (b) (4) The statement of identity should be written as originally edited by the review team in the November 22, 2016 information request,

Epinephrine Inhalation Aerosol
0.125 mg per spray
Bronchodilator

The text should be in bold type and in white font, so that the text can easily be seen on the PDP since the background is a dark brown.

2. The sponsor should place "Suspension", with a colon, before the (b) (4) statement on the PDP. It should be written as follows:

Suspension:
(b) (4)

Required changes to the outer Carton drug facts label

1. The Drug Facts labeling did not include the barlines and hairlines required by 21 CFR 201.66(d)(8). The sponsor should refer to 201 CFR 201.66(d)(8) and 21 CFR Appendix A to Part 201 for formatting information in Drugs Facts. An example of a standard labeling format with the required barlines and hairlines can be seen in 21 CFR Appendix A to Part 201.

2. The sponsor should submit complete Drug Facts font specifications. See 21 CFR 201.66(d) and Guidance for Industry – Labeling OTC Human Drug Products (Small Entity Compliance Guide) May 2009. When the sponsor submits new labeling because of a proprietary name change, complete Drug Facts font specifications should be submitted.

3. Under the asthma alert, the bullet in front of the statement "These may be signs that your asthma is getting worse" Should be removed. There should be a period at the end of the statement per 21 CFR 341.76(c)(6)(F).

4. Under ***Directions,*** the instruction for washing the mouthpiece should be written on the DFL as [redacted] (b) (4)

Required changes to the immediate container label

1. [redacted] (b) (4)

2. The statement of identity reads, Epinephrine Inhalation Aerosol [redacted] (b) (4) The text should be black font and bolded. The statement of identity should be edited as follows:

   Epinephrine Inhalation Aerosol
   0.125 mg per spray
   Bronchodilator

3. In the Active Ingredient heading, in parenthesis in states [redacted] (b) (4) The statement should be edited to "in each spray."

4. The statement [redacted] (b) (4) should be included under the **Directions** heading.

5. There is a Warning statement to (b) (4)

Required changes to the consumer information insert

1. Under section B. (b) (4)

2. Under section C. (b) (4) for consistency in the labeling.

Required changes to the website

1. On the first webpage for the website (b) (4) was added to the statement of identity. The sponsor should delete (b) (4) from the statement of identity.

2. On the DFL page, under the asthma alert, there is a bullet in front of the statement "These may be signs that your asthma is getting worse." The bullet should be removed and a period should be placed at the end of the statement.

3. Under ***Directions***, the instruction for washing the mouthpiece should be written on the DFL as (b) (4)

4. The text used on the website should be consistent with the language recommended on the PDP, the Drug Facts labeling for the outer container, and the consumer information insert. So edits should be done, where applicable.

IV. SUBMITTED LABELING

The labels of the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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/s/

MICHELLE D WALKER
12/22/2016

STEVEN A ADAH
12/22/2016

LABEL, LABELING, AND HUMAN FACTORS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 6, 2016
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 205920
Product Name and Strength:	Primatene Mist (Epinephrine) Inhalation Aerosol, 0.125 mg per inhalation
Product Type:	Single Ingredient, Combination Product
Rx or OTC:	OTC
Applicant/Sponsor Name:	Armstrong Pharmaceuticals, Inc.
Submission Date:	June 28, 2016
OSE RCM #:	2016-1526
DMEPA Primary Reviewer:	Grace P. Jones, PharmD, BCPS
DMEPA Associate Director:	Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

Armstrong Pharmaceuticals intends to market Primatene Mist (epinephrine inhalation aerosol) containing the hydrofluoroalkane (HFA-134a) propellant, under NDA 205920. The Applicant received a Complete Response (CR) letter on May 22, 2014 and resubmitted their application in response to the CR letter on June 28, 2016. As advised in the CR letter, the Applicant conducted a human factors (HF) validation study using a placebo-filled intend to market product and the revised Instructions for Use (IFU) and included the results in this submission.

This review evaluates from a medication error perspective the human factors (HF) validation study report, the proposed IFU for Primatene Mist, as well as the container label and carton labeling. Our analysis of the findings from the HF validation studies informed our review of the proposed IFU, container label, and carton labeling.

1.1 REGULATORY HISTORY AND BACKGROUND

Primatene Mist (epinephrine) inhalation aerosol was approved on November 8, 1967, under NDA 016126 and was originally marketed by Wyeth Consumer Healthcare, as an OTC product indicated for the temporary relief of occasional symptoms of mild asthma. Armstrong Pharmaceuticals, Inc. had been the contract manufacturer of Primatene Mist for Wyeth from 2004 to 2008. On July 8, 2008, Armstrong Pharmaceuticals, Inc. acquired Primatene Mist (epinephrine) inhalation aerosol from Wyeth and marketed the product until December 31, 2011, when it was withdrawn from distribution due to the phase out of chlorofluorocarbons (CFC) outlined in the Montreal Protocol. Since then, the Applicant has re-formulated the epinephrine inhalation aerosol using HFA-134a (hydrofluoroalkane) as the propellant. On July 20, 2013, the Applicant submitted the re-formulated epinephrine HFA inhalation aerosol for review under NDA 205920. On May 22, 2014 the application received a Complete Response letter, and then on June 28, 2016, the Applicant resubmitted their application in response to the Complete Response letter.

In addition to the different propellant used in the original CFC Primatene Mist compared to the currently proposed HFA Primatene Mist product, other product differences are noted in Table 1.

Table 1. Comparison of original CFC Primatene Mist and the currently proposed HFA Primatene Mist (From DailyMed https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=13423 and submission dated June 28, 2016)

Proprietary Name	Primatene Mist (previously marketed CFC product)	Primatene Mist (proposed HFA product)
Propellant	**CFC** – phased out December 31, 2011	**HFA**
Drug Container	Glass reservoir	Aluminum canister
Dose indicator	Semi-transparent reservoir	Attached dose counter
Formulation	Solution	Suspension
Use Instructions	(b) (4) mouthpiece after each use	(b) (4)

Proprietary Name	Primatene Mist (previously marketed CFC product)	Primatene Mist (proposed HFA product)
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; max 8 inhalations/per day
	DRUG FACTS LABEL	
Strength	0.22 mg per inhalation	0.125 mg per inhalation
Uses	For temporary relief of occasional symptoms of mild asthma: wheezing, tightness of chest, shortness of breath	For temporary relief of mild symptoms of intermittent asthma: wheezing, tightness of chest, shortness of breath
Warnings	Asthma alert Because asthma can be life threatening, see a doctor if you: ▪ are not better in 20 minutes ▪ get worse ▪ need 12 inhalations in any day ▪ use more than 9 inhalations a day for more than 3 days a week ▪ have more than 2 asthma attacks in a week	Asthma alert: Because asthma may be life threatening, see a doctor if you ▪ are not better in 20 minutes ▪ get worse ▪ need more than 8 inhalations in 24 hours ▪ have more than 2 asthma attacks in a week ▪ These may be signs that your asthma is getting worse (b) (4)
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 1minute. If not relieved, use once more. Do not use again for at least 3 hours. Children under 4 years of age: ask a doctor	(b) (4) Do not use more than directed Adults and children 12 years of age and over: ▪ 1 to 2 inhalations for each dose ▪ Start with one inhalation, wait at least 1 minute. If not relieved, (b) (4) ▪ Wait at least 4 hours between doses ▪ Do not use more than 8 inhalations in 24 hours Children under 12 years of age: do not use; it is not known if the drug works or is safe in children under 12.

Of note, the Applicant had submitted the proprietary name (b) (4) for review on June 30, 2016, however, DMEPA held a teleconference with the Applicant to discuss concerns surrounding the proposed proprietary name and alternative naming options. Thus on September 19, 2016, the Applicant submitted the proposed proprietary name, Primatene Mist for review which DMEPA found acceptable (see DARRTS, Proprietary Name Review dated 11/2/2016).

2 MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review. The Appendices provide the methods and results for each material reviewed.

Table 2. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 HUMAN FACTORS VALIDATION STUDY

A human factors (HF) validation study was conducted to evaluate whether the proposed HFA epinephrine inhalation aerosol inhaler device and the proposed Instructions for Use (IFU) support the safe and effective use of the proposed product by consumers in the OTC setting. We recognize that the functionality and user interface of the proposed HFA inhaler device differs from that of the original Primatene Mist CFC inhaler device, whereas the intended user environment, the OTC marketplace, has remained the same. The product user interface of the proposed product now resembles currently marketed prescription HFA metered dose inhalers (MDIs). The Applicant submitted the following HF validation study reports:

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

The HF Engineering Report provides qualitative data from the HF validation study. Although we acknowledge the statistical quantitative HF report, our review of the HF validation study primarily focused on the qualitative data provided in the HF Engineering Report. We defer to our biostatistician colleagues' review in the Office of Biostatistics for the analysis of the statistical data.

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

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

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

Completed (C): participants successfully performed the use task and demonstrated an understanding of the communication objective

Completed with Issues (CI): participants successfully performed the use task and demonstrated understanding of the communication objective but either struggled initially to do so, self-corrected during the testing session, or completed the task in such a way that differs from the IFU, and after being referred to the instructions by the study moderator, successfully performed the task and demonstrated understanding

Not Completed (NC): participants did not complete the task successfully or demonstrated understanding of the communication objective.

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

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

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

Correct (C): participants independently and without prompting articulated a correct understanding of the communication objective and described a correct strategy for achieving that objective

Not Correct (NC): participants did not articulate a correct understanding of the communication objective or described a correct strategy for achieving that objective.

Our evaluation of the HF validation study identified deficiencies associated with the study design:

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

Human Factors Study Results Assessment

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

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[a] Applying Human Factors and Usability Engineering to Medical Devices, available online at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

[b] Participants were divided into user groups consisting of 132 Adult participants (79 women and 72 men), 19 Juvenile participants. Of these there were 24 Low Literate Adults (3 of the 19 juveniles tested at below grade literacy levels), 39 Prior Inhaler Experienced participants (which included products such as, albuterol, Flovent, dry powder inhalers, Advair, Dulera, Symbicort, Xopenex, Pulmicort, and nebulizers), and 8 participants had prior Primatene Mist experience.

Initial Priming Errors (Task 1)

For the initial priming task, there were 46 use errors reported, including 8 participants with scores of NC and 38 participants with scores of CI. See Table 3 for the distribution of use errors based on the user groups.

Table 3. Initial priming of the inhaler – Distribution of use errors by user group

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

All 46 of these participants failed to correctly perform the "shake and spray" subtask in the overall initial priming task. To complete this task, the IFU instructs the user to shake the inhaler then spray the inhaler into the air and repeat this 4 times. A description of the use errors are as follows:

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

The Applicant indicated in the submission that in parallel with the formative HF study, they conducted bench studies to further evaluate the effect and potential risk if the initial priming steps are not performed according to the instructions in the IFU (i.e., shaking and spraying the inhaler in sequence for a total of 4 times). The initial priming bench study results showed that if the initial priming is performed by 1 shake followed by 4 or 5 consecutive sprays as long as the

duration of the priming sequence does not exceed 10 seconds, then there would be minimal risk of diminished safety and effectiveness of the proposed inhaler device. The Applicant also notes that if the initial priming use error occurs in the real OTC use environment, whereby the inhaler is not primed for first use, then the first 3 or 4 inhalations would essentially serve to prime the inhaler.

Of the 46 errors described above, there were 35 participants who did not follow the initial priming sequence as described in the IFU, but they **shook the inhaler at least one time**, which allows for the epinephrine aerosol suspension to become uniform. Twenty-six (26) of these participants met the criteria of the bench study, performed the priming in an acceptable sequence, or self-corrected independently during the simulated use task and received scores of CI. However, eleven (11) participants **did not shake** the inhaler during the initial priming task. Six (6) of these participants received scores of CI indicating they did not shake the inhaler during the initial priming task but later self-corrected, thus, feasible that these participants were referred to the instructions during the simulation. The applicant indicated that not shaking the inhaler can affect drug content uniformity of the proposed inhaler device. Table 4 provides details of the participants who did not shake the inhaler in the initial priming task based on user groups. Of note, only 2 of these 11 participants were previous users of the formerly marketed CFC Primatene Mist product.

Table 4. Subtask not shaking the inhaler in the initial priming task – Distribution by user group

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

DMEPA's analysis of the study results determined that, after all acceptable mitigations including mitigations from the Applicant's bench testing results were applied, 13% of participants (20 participants out of 151 total participants) failed this initial priming task 1 (see details in Appendix C, table 8).

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

Given the subjective feedback for this initial priming task, we have provided recommendations to increase the clarity and readability of this section in the IFU, which is provided in Section 4.1 below.

Cleaning the inhaler Errors (Task 2)

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

Of the 56 participants who did not clean the inhaler according to the IFU but self-corrected during the simulated use task, 52 participants did not wash the inhaler for at least 15 seconds, and 12 participants did not remove the drug container.[c] Of the 4 participants with scores of NC who failed the task, 3 did not remove the container so that the mouthpiece could be washed nor did they demonstrate understanding that washing the inhaler prevents clogging, and 1 participant did not wash the mouthpiece despite demonstrating understanding of the need to wash the inhaler. Table 5 provides the distribution of use errors based on the user groups.

Table 5. Cleaning the inhaler – Distribution of use errors by user group

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

DMEPA's analysis of the study results determined that, after all acceptable mitigations including mitigations from the Applicant's bench testing results were applied, 12% of participants (18 participants out of 151 total participants) failed this initial priming task 1 (see details in Appendix C, table 9).

The provided root cause analysis for the use errors included the following, a lack of awareness of the need to clean the inhaler resulting from a failure to read the instructions for use prior to completing the task and a negative knowledge transfer from prior inhaler experience and abnormal use. Additionally, there were 15 use errors in the twist and pull out container subtask, and 23 use errors in the wash either end, running water subtask. Therefore, we provide recommendations to increase the clarity and readability of the IFU in Section 4.1 below.

[c] Participants were listed twice if they experienced both kinds of use errors during the simulated use task prior to self-correcting (i.e., not washing the inhaler for at least 15 seconds and not removing the drug container). Therefore, the number of use errors equaled more than 56.

Routine use of the inhaler Errors (Task 3)

For the routine use task, there were 23 use errors reported, including 2 participants with scores of NC and 21 participants with scores of CI. This task required participants to re-prime the device by removing the cap, shaking and spraying once, with finger on center of the top of the inhaler container while not placing inhaler in the mouth, and then delivering an inhalation and replacing the cap. Two (2) participants did not re-prime the inhaler at all and failed the task (saw the instructions but chose not to re-prime), eight (8) participants initially failed the task but eventually self-corrected after being referred to the instructions, eight (8) saw the instructions but did not complete them as directed, one (1) did not read the IFU, and four (4) self-corrected independently. See Table 6 for the distribution of use errors based on the user groups.

Table 6. Routine use of the inhaler – Distribution of use errors by user group

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

DMEPA's analysis of the study results determined that, after all acceptable mitigations were applied, 13% of participants (19 participants out of 151 total participants) failed this initial priming task 1 (see details in Appendix C, table 10).

The provided root cause analysis indicated that some use error participants did not read the IFU. The use errors seen in the routine use of inhaler task are similar to the use error for task 1, initial priming. Therefore, for consistency we provide similar recommendations to this section to increase clarity of important information in the IFU, which is provided in Section 4.1 below.

Interpreting the dose indicator (Comprehension Task 4)

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

Do not rely on dose indicator if inhaler dropped (Comprehension Task 5)

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

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

Correctly hold the inhaler (Comprehension Task 6)

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

3.2 OVERALL ASSESSMENT

The HF study failed to demonstrate that the proposed HFA inhaler device can be used safely and effectively by the intended users. There were errors in the HF study particularly related to the simulated use tasks which can lead to medication error risks when the inhaler is used improperly, including overdose, underdose, or lack of efficacy. DMEPA's analysis of the HF study results determined that for the 3 simulated use tasks after all acceptable mitigations were applied, there were 20 failures for Task 1 Initial Priming (20/151, 13%), 18 failures for Task 2 Cleaning the Inhaler (18/151, 12%), and 19 failures for Task 3 Priming for Routine Use (19/151, 13%), which led to a total of 57 task failures (57/151, 38%). Moreover, based on these results we determined that there were 30% of participants (45/151) who failed at least one task. Thus we discussed this with the DNDP Medical Officer and with Office of Pharmaceutical Quality (OPQ) to determine the clinical significance of these risks.

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

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

2) Not cleaning the inhaler device properly may lead to underdose or lack of efficacy

   We acknowledge the Applicant's data supporting that the inhaler can be washed for at minimum 2 seconds versus the 30 seconds as indicated in the IFU. Despite this, there were 4 participants who washed the inhaler for less than 2 seconds. Thus, there is

residual risk of consumers not cleaning the inhaler sufficiently which can lead to the delivery of reduced product or no drug product during use, constituting an underdose. Based on our discussion with OPQ, the continued use of a clogged inhaler would result in a suboptimal actuation and reduced potency of the drug product. In this event, consumers would receive an underdose, and may experience a lack of efficacy. However, based on further discussion with the Medical Officer, it may be expected that consumers would attempt to reuse the inhaler or seek medical attention if asthma symptoms are not relieved in 20 minutes, as instructed by the Drug Facts Label.

3) Not comprehending the Dose Indicator or what to do if the inhaler were dropped may lead to lack of efficacy

   We acknowledge the Applicant's data supporting that the inhaler and the dose indicator are unlikely to malfunction if dropped (0.08% chance of malfunction). However, the concept of a dose indicator is new to the OTC marketplace and despite the Applicant's bench data, 2 participants could not interpret the dose indicator. If consumers do not comprehend the purpose of the dose indicator, they may continue to utilize the inhaler when in fact no more actuations remain, thus, consumers would experience a lack of efficacy. In terms of clinical significance to this risk, similar to not cleaning the inhaler device properly, we can anticipate if consumers' asthma symptoms are not relieved with the proposed product, based on the proposed product's labeling, consumers would seek medical attention.

The failed results from the HF validation study demonstrate that residual risks related to improper priming, shaking and cleaning of the inhaler device may lead to medication errors including overdose, underdose, and lack of efficacy. Based upon the use errors reported, we provide recommendations in Section 4.1 to improve clarity of the IFU and improve the product-user interface which may decrease the risk of medication error. However, we are unable to conclude that any labeling mitigation would eliminate the potential for medication errors entirely. We are aware of post-marketing errors with prescription HFA MDI products with similar product-user interfaces, despite their use under a prescriber's supervision. The known use errors with prescription HFA MDIs include not shaking the inhaler before each dose[d] and not properly cleaning the inhaler device. We note these known use errors are similar to those use errors observed in the proposed product HF study, thus we anticipate use errors for the proposed product to be similar to those observed with the prescription products, if approved. However, we acknowledge that the introduction of the proposed product into the OTC marketplace would be representative of a first in class HFA MDI into the OTC space. Consumers are expected to use this proposed product relying on the product's labeling without any external (i.e., healthcare professional) assistance. We defer to the Review Division to determine if the residual risks (overdose, underdose, lack of efficacy) of the proposed HFA MDI user interface and their clinical consequences are acceptable for the OTC marketplace.

[d] Institute for Safe Medication Practices. Correct use of inhalers: Help patients breathe easier. ISMP Nurse Advise ERR ISMP. 2016; 14(9):1-2.

3.3 LABELS AND LABELING

Our review indicates that the proposed carton labeling can be improved to increase clarity of important information. In addition, our recommendations to revise the proposed IFU also pertain to information in the proposed carton labeling. Therefore to provide consistency in information provided in the carton labeling and the IFU, we provide our recommendations in Section 4.1.

4 CONCLUSION & RECOMMENDATIONS

We conclude the HF validation study was unable to demonstrate that the intended user population is able to use the product safely and effectively. The failures noted in the HF study would result in patients receiving either an overdose or an underdose potentially resulting in lack of efficacy. Thus, we provide labeling recommendations in Section 4.1 for the applicant to implement corrective and preventative measures to improve the product-user interface that may decrease this risk. However, in light of our post-marketing experience with similar prescription HFA MDIs, we anticipate that these changes are unlikely to eliminate the risks altogether. We defer to the Review Division for determination of whether the benefits of introducing this epinephrine inhalation product with its proposed HFA MDI user interface outweighs the risk for use errors that can result in improper dosing.

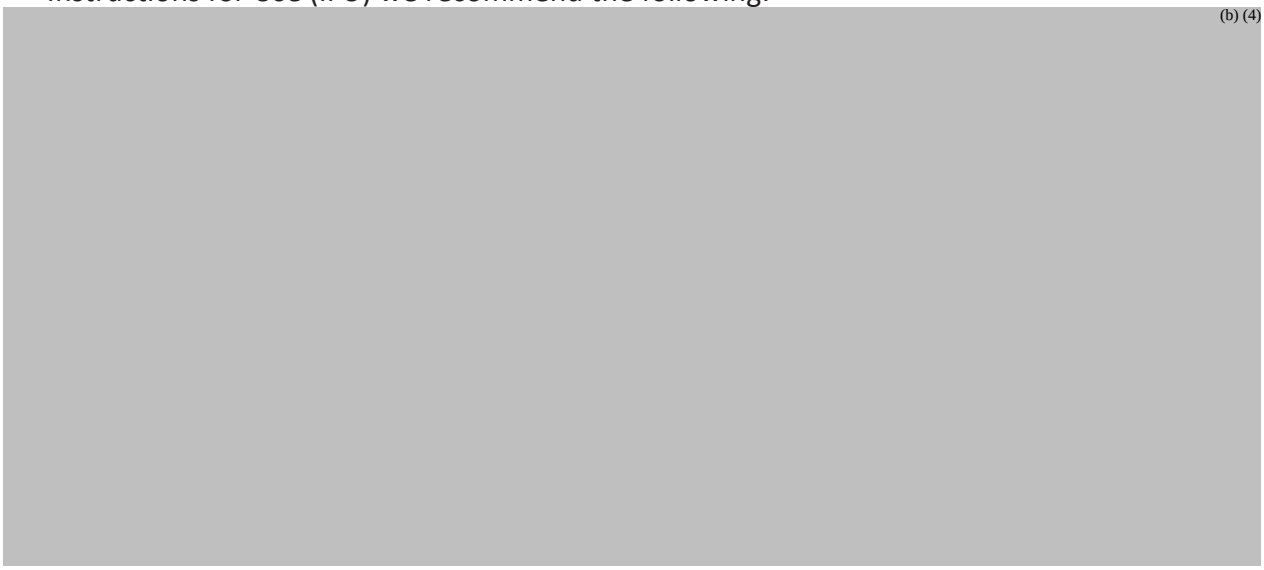
We provide recommendations for the Instructions for Use (IFU) in section 4.1 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Instructions for Use

To improve clarity, readability, and consistency of important information in the Instructions for Use (IFU) we recommend the following:

(b) (4)



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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 7 presents relevant product information for Primatene Mist that Armstrong Pharmaceuticals, Inc. submitted on June 28, 2016.

Table 7. Relevant Product Information for Primatene Mist	
Initial Approval Date	N/A
Active Ingredient	Epinephrine
Indication	For temporary relief of mild symptoms of intermittent asthma: wheezing, tightness of chest, shortness of breath
Route of Administration	Oral inhalation
Dosage Form	Aerosol
Strength	0.125 mg per inhalation
Dose and Frequency	Adults and children 12 years of age and over: 1 to 2 inhalations for each dose. Start with one inhalation, wait at least 1 minute. If not relieved (b) (4) Wait at least 4 hours between doses. Do not use more than 8 inhalations in 24 hours. Children under 12 years of age: do not use; it is not known if the drug works or is safe in children under 12.
How Supplied	Container of 160 inhalations
Storage	Store at room temperature, between 15-25°C (59-77°F)
Container Closure	The container consists of: 14 mL pharmaceutical aerosol can, (b) (4) The valve consists of: (b) (4) Aluminum Anodized Valve, (b) (4) 50 □L metering (b) (4) (b) (4) The actuator/cap consists of: (b) (4) L shape actuator with a (b) (4) orifice; assemble to a (b) (4) cap. Drawing No. (b) (4) (actuator) (b) (4) (cap) The dose counter consists of: (b) (4) Top Mount Actuation Indicator (Model number (b) (4), Part No. (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 26, 2016, we searched the L:drive and AIMS using the terms, Primatene Mist to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previously completed Proprietary Name Review for Primatene Mist.[e] We have not reviewed labels, labeling, or human factors studies for NDA 205920.

[e] Jones, G. Proprietary Name Review for Primatene Mist NDA 205920. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 11 01. RCM No. 2016-10269700.

APPENDIX C. HUMAN FACTORS STUDY

Quantitative Analysis Report for Human Factors Study and the Human Factors Engineering Report

C.1 Study Design

Purpose of study:

- Validate the usability of device by following the IFU intended to be used in the OTC setting
- Usability characterized by:
    - User interface:
        - device set-up (assembly)
        - device use (initial priming and re-priming and routine use)
        - device cleaning
    - Effectiveness
    - Efficiency
    - Ease of user learning
    - User satisfaction

Study Methodology:

- Test participants represented the simulated users of the device.
- All critical tasks are performed during the test.
- Device user interface represents the final design.
- Test conditions are sufficiently realistic to represent actual conditions of use.
- Participants familiarized with product (given product packaged in carton with IFU), then asked to perform a series of simulated use tasks, and then asked open-ended questions to assess understanding of the device labeling (IFU) to identify root cause for failures

6 Tasks: 3 critical behavioral tasks, 3 labeling HF questions (based on known use problems)

Primary endpoints

1) Initial priming
2) Cleaning to prevent clogging
3) Routine use of inhaler

Secondary endpoints

4) How to interpret dose indicator (Red Zone indictor, dose indicator moves q 20 sprays)
5) Not relying on dose indicator if dropped
6) Understand correct finger positioning required to ensure that the device expels medication properly with each spray

For critical tasks 1 through 3, participants were given a prompt that described a use scenario and were asked to demonstrate how they would use the inhaler in that scenario.

- The study moderator did not provide any assistance, prompting, or coaching.
- Participants were able to consult the instructions provided in the Package Insert IFU at any time, if they chose to do so.

- As the participants completed each simulated use scenario, the moderator asked if they believed they had completed the scenario successfully, but did not provide any feedback to the participant.
- During simulated use, the moderator recorded participant behavior and comments, if any, and objectively scored participants on the completion of each task and subtasks using scores of Completed (C), Completed with Issues (CI), and Not Completed (NC)

Training:

- No training was provided to the participants
- Participants were given the product packaged in its carton with the package insert IFU and given an opportunity to familiarize themselves with the product

Study Procedures:

- Participants were given use scenario tasks and asked to demonstrate how they would use the inhaler in that scenario
- Participants could refer to the IFU for assistance
- Once participants completed each simulated use task, the moderator asked the participant if they believe they have competed the task successfully, but did not provide feedback
- Following the simulated uses tasks, participants were asked open-ended questions to assess understanding of the remaining 3 tasks
- Juvenile participants (12 to 17 years of age) were accompanied by a parent or guardian. The parent/guardian accompanied the juvenile into the test session if in real life situations they normally assist their child with medical products and the parent/guardian provided assistance with the simulated use task if the juvenile needed help to complete the task.

Objective performance scoring for critical behavioral tasks (CBTs)

- Completed (C): successfully performed use task and demonstrated understanding of the communication objective
- Completed with issues (CI): successfully performed the use task but struggled initially or self-corrected, or completed task in a varied way from the IFU directions
- Not completed (NC): did not successfully perform use task or demonstrate understanding of the communication objective

Objective performance scoring for labeling HF questions

- Completed (C) or
- Not completed (NC)

Statistical endpoints:

- Lower limit of 95% confidence interval (CI) of all 3 CBTs were greater than 85%, then statistically significantly greater than 85%
- 85% Acceptable rate using the lower limit of the 95% Confidence Interval (LLCI)
- Applicant states that all acceptable rates and their lower limits of 95% exact CI were above 85% for all 6 tasks The 6 CBT & ALHFQs + 60 sub-tasks were evaluated, observed, and scored
- Acceptable Rates (AR) were calculated based on performance score
- 2-sided 95% confidence interval of the AR for CBT & ALHFQs were calculated

Risk Based Evaluation Datasets and Bench Studies:

- A Risk-Based Evaluation (RBE) was conducted in order to incorporate learnings from related bench testing. The resulting RBE dataset (RBED) was used for primary analysis in this study. During the priming process, shaking of the inhaler ensures that the medication is evenly mixed and distributed throughout the canister. If the step is not performed (neither shaking nor spraying), it could create an uneven distribution of the ingredients during the subsequent actuation, in such cases the product may not provide a full dose during the inhalation. If the user does not perform priming a total of four times, the subsequent uses of the product may not provide full doses during the inhalation.
- In task 1, initial priming, end-users who did not carefully read the IFU, performed the initial priming process as one shake followed by 4 or 5 continuous sprays, which is a deviation from the IFU. A series of bench studies were conducted to evaluate the effect and potential risk in cases where the initial priming steps were not performed per label instructions. These studies showed that the use-related risk for safety and effectiveness would be minimal if the initial priming was performed by one (1) shake followed 4 to 5 consecutive sprays as long as the duration of these sprays was no more than ten (10) seconds. Bench studies 6 and 7 were related to the effect of initial priming on dose content uniformity. The risk of deviating from the labeled initial priming instructions may affect dose content uniformity of the first and second inhalation after the initial priming procedure, but the bench studies showed that dose content uniformity also depends on the duration of the shake and multiple spray procedure, and the initial priming has no effect on dose content uniformity for the third inhalation through the last inhalation (canister life).
- Task 2 evaluated washing the device to prevent clogging. Bench studies 3, 4, and 5 were related to device cleaning studies.
    - Bench study 3 was designed to test the robustness of the instructed cleaning procedure on the package insert IFU. The study tested various wash frequencies, cleaning procedures and durations of the cleaning process to assess the effectiveness of these procedures to prevent clogging. The study results showed that variations in the cleaning procedure have no impact on the effectiveness of cleaning. Specifically, the results show that: 1) actuators can be used for 2 days without cleaning, 2) variations in the orientation of inhaler during rinse have no impact, 3) variations in the duration of rinse (from 15 to 30 seconds) have no impact, and 4) variations in the water temperature (from room temp to 40°C) have no impact.
    - Bench study 4 was a supplement to test worse-case scenario that included 3 days of use, 15 seconds duration of rinse and lower water temperature (10°C) as cleaning procedures. The study result shows no impact on effectiveness of cleaning.
    - Bench study 5 was a supplement to test extreme worse-case scenario and different cleaning methods showed no impact to cleaning effectiveness, specifically, 1) extremely short duration of rinse (2 seconds) has no impact, 2)

different drying method by using paper towel or lint-free cloth has no impact, and 3) different rinsing method by rinsing with hot soapy water has no impact.

Requirements for successful performance/understanding of critical tasks (from the Human Factors Engineering Report, p.113-114):

Task Description	Successful Performance Requirements
1a. Initial priming of the inhaler to prepare it for use.	Initial Prime: • Remove the cap • Shake and spray the inhaler into air, repeat process 4 times • Finger on center of Dose Indicator • Spray into air, not mouth
1b. Take an Inhalation	Deliver an inhalation: • Hold inhaler in correct orientation • Squeeze mouthpiece and container together while inhaling • Take a deep breath/mouth closed
2. Wash to prevent clogging	• Remove container from mouthpiece • Remove the cap • Wash either end under running water for 15 seconds* • Place container back in mouthpiece correctly • Container fully seated in place
3. Routine use of the inhaler (i.e., taking a dose/puff)	Prime: • Remove the cap • Shake and spray into air 1 time • Finger on the center of the Dose Indicator • Understands the importance of pressing with a finger in the center of the Dose Indicator to ensure a proper spray • Spray into air, not mouth Deliver an inhalation: • Hold inhaler in correct orientation • Squeeze mouthpiece and container together while inhaling • Take a deep breath/mouth closed
4. Interpreting the dose indicator	• Understand the meaning of the Red Zone on the Dose Indicator
5. Do not rely on the dose indicator if the device has been dropped	• Understands not to rely on the Dose Indicator if the inhaler has been dropped and/or would behave appropriately to avoid the risk of the inhaler running out without a Red Zone warning
6. Correct Finger Position for taking an inhalation	• An understanding of the correct finger position required to ensure that the device expels medication properly with each spray

*Success requirement of running water through the mouthpiece for at least 15 seconds differs from the direction in the IFU to rinse for 30 seconds. This difference is based on Applicant's additional bench testing of the robustness of the cleaning procedure (which they state was done prior to the Validation Study). The study results demonstrated that variations in the duration of rinsing (from 15 to 30 seconds) had no impact on the effectiveness of cleaning. The IFU specifies 30 seconds in order to encourage users to meet the shorter 15 second minimum requirement.

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C.2 Results

Overall Results:

Summary of statistical analysis results for Critical Behavior Tasks and Additional Labeling Human Factor Questions (from Quantitative Analysis Report for Human Factors Study, p.4):

CBT/ALHFQ	# of Paticipants (TEP*)	Global Results				Lower Limit of 95% confidence Interval, %		
		C	CI	NC	Acceptable Rate, %	Exact Method	>85%?	Normal Approximation
Critical Behavioral Tasks (CBT)								
Task 1 First Use	151	105	38	8	94.7%	89.8%	√	91.1%
Task 2 Cleaning	151	91	56	4	97.4%	93.4%	√	94.8%
Task 3 Routine Use	151	128	21	2	98.7%	95.3%	√	96.9%
Additional Labeling Human Factor Questions (ALHFQ)								
Question-4 Dose Indicator	151	149	-	2	98.7%	95.3%	√	96.9%
Question-5 Dropped Device	151	147	-	4	97.4%	93.4%	√	94.8%
Question-6 Hold Inhaler Properly	151	151	-	0	100.0%	97.6%	√	100.0%
All Tasks/Questions	151				97.8%	94.1%	√	95.7%

*T EP: Task-Evaluable Population; C: Completed (for CBT 1-3) or Correct (for ALHFQ 4-6);
CI: Complete with Issues (for CBT 1-3); NC: Not Completed (for CBT 1-3) or Not Correct (for ALHFQ 4-6).

Task 1: Initial Priming:

Statistical analysis results (from Quantitative Analysis Report for Human Factors Study, p.43):

Detailed Items for Human Factors	# of Participants (TEP*)	Global Results				Lower Limit of 95% confidence Interval, %		
		C	CI	NC	Acceptable Rate, %	Exact Method	>85%?	Normal Approximation
Task-1 Performance, Overall	**151**	**105**	**38**	**8**	**94.7%**	**89.8%**	√	**91.1%**
1a Initial Prime the device	**151**	**105**	**38**	**8**	**94.7%**	**89.8%**	√	**91.1%**
1) Remove cap	151	151	0	0	100.0%	97.6%	√	100.0%
2) Overall Shake & Spray	151	105	38	8	94.7%	89.8%	√	91.1%
3) Finger on center	151	151	0	0	100.0%	97.6%	√	100.0%
4) Not in the mouth	151	151	0	0	100.0%	97.6%	√	100.0%
1b Deliver an Inhalation	**151**	**150**	**0**	**1**	**99.3%**	**96.4%**	√	**98.0%**
1) Hold inhaler in correct orientation	151	151	0	0	100.0%	97.6%	√	100.0%
2) Squeeze while inhaling	151	151	0	0	100.0%	97.6%	√	100.0%
3) Deep breath/ mouth closed	151	150	0	1	99.3%	96.4%	√	98.0%
1c Replace cap	**151**	**151**	**0**	**0**	**100.0%**	**97.6%**	√	**100.0%**

- N=8 had scores of not completed (NC), did not correctly complete required initial priming procedure independently or demonstrated understanding of initial priming process or perform task correctly after being referred to IFU
- N=6 had been assigned NC, but were changed to CI after risk-based evaluation

- These participants shook and sprayed 4 or 5 times in less than 10 seconds (bench studies showed use-related risk for safety and effectiveness would be minimal if initial priming performed by one shake followed by 4 or 5 consecutives sprays as long as the duration was no more than 10 seconds)

- N=38 (completed with issues), self-corrected at some point during the simulation without prompting, or demonstrated understanding and correctly performed the task after being referred to the IFU
- Subtask 1b-deliver an inhalation – deep breath/mouth closed, 1 participant did not correctly perform the inhalation

Qualitative data from the Human Factors Engineering Report:

Not Completed (NC) use errors observed with Task 1 – Initial priming of the inhaler (n=14):

N	Use Error
7*	Participant shakes the inhaler 1 time and then sprays into the air 4 or 5 times in immediate sequence without shaking the inhaler in between each spray into the air, as directed in the Package Insert IFU.
3	Participant does not shake the inhaler, but sprays into the air 3 or less times.
2	Participant takes an inhalation without any attempt to prime first. They do not shake the inhaler or spray it into the air before dosing.
2	Participant removes the medicine container to shake.

*6 of these participants were recoded from NC to CI based upon their shaking and spraying 4 or 5 times within 10 seconds. 1 participant, was not recoded because they took longer than 10 seconds which may not deliver a complete dose for subsequent sprays.

Distribution of use issues by user group:

User Group		Not Completed (NC)	Completed with Issues (CI)	Total use issues per user group
Adult – Normal Literacy	Inhaler Experienced	2	4	6
	Inhaler Naive	1	23	24
Adult – Low Literacy	Inhaler Experienced	2	4	0
	Inhaler Naive	2	5	7
Juvenile	Inhaler Experienced	1	2	3
	Inhaler Naive	0	2	2
Total use issues		8	38	46

Root Cause – Failure to read or refer to the IFU prior to completing the task:

- N=5 had scores of not completed (NC)
- N=1 had score of completed with issues (CI)
- Narrative examples:
  - *During the familiarization period, he read the Package Insert IFU while it was still folded. He could only see Panel 1 of Side 1 containing the* (b) (4) *He then looked at Side 2 of the instructions and read Sections C* (b) (4) *and* (b) (4) *During his*

simulation, he removed the container from the mouthpiece, shook the container, reassembled the inhaler and sprayed into air one time. After the moderator referred him to the instructions, he appeared to have difficulty understanding the instructions

- o t*rying to go off the picture instead of reading the instructions"*
- o *I'm not a good person with routines. I might shake once and spray four times and other times I might not shake, but would spray four times."*
- o P*articipant read the instructions and shook once and sprayed 4 times. After the moderator directed him to the text graphic in the box below Step 4, the participant noted that he had misinterpreted Step 4 and had not read the panel at the bottom. He apparently had never noticed this box until shown by the moderator.*
- o *Was "looking at the cheat sheet" i.e., the* (b) (4) *Panel She said that she was "looking at the cheat sheet" (i.e., the* (b) (4) *Panel, see below) of the IFU prior to completing the task because "I don't have patience for details" and for the longer section that provides first time use instructions. When asked to complete the task again during the post-simulation interview, the participant again shook once and sprayed 4 times because "I assumed that's what you're supposed to do". The moderator asked her to re-review the instructions and still she thought one shake and four sprays in a row was correct.*
- o *During the post simulation interview, the moderator asked him to review the instructions. He completed the task again after reviewing Step 4, this time shaking once and spraying four times into the air.*

Root Cause – Negative transfer based on prior inhaler experiences

- N=3 had scores of not completed (NC)
- Narrative examples:
  - o *When the moderator referred the teen back to the instructions, both he and his mother interpreted the language in Step 4* (b) (4) *As repeat the act of spraying only four times.*
  - o *This person also did not read the IFU before task (functionally illiterate)*

Root Cause – Confusion caused by the presentation of instructions in the IFU

- N=4 had scores of completed with issues (CI)
- Narrative examples:
  - o *Adult experienced participant noted that he had only looked at Step 4* (b) (4) *and said that he did not look at the images located in the boxes below the instruction. He interpreted the sentence to mean shake once and spray 4 times*
  - o *Moderator asked participant to look at the images under Step 4 and she responded that it said* (b) (4)
  - o *Only using the images in the box on the left side and did not attend to the text in the box on the right side, said eye went to the left column because that is how one reads*

- *"Just one line of verbiage [redacted] (b) (4) [redacted] Maybe it takes up too much space on the instructions. I think having to pump it four times is a bit excessive. Especially if I'm in a situation where I feel like I really need it."*

Root Cause – Understood the instructions but chose not to comply

- N=1 had score of not completed (NC)
- Narrative Example:
  - *Participant noted that he only focused on Step 4 (see image x above) and did not read the graphics. He also noted that adding "four separate times" would make it more understandable*

Completed with Issues (CI) use errors observed with Task 1 – Initial priming of inhaler (N=32):

N	Use Error
16	Participant shakes the inhaler 1 time and then sprays into the air 4 times in immediate sequence without shaking the inhaler in between each spray as directed in the IFU
6	Participant shakes the inhaler and sprays into the air fewer than 4 times in immediate sequence before taking an inhalation
2	Participant does not shake the inhaler, but sprays into the air 1 or more times
4	Participant does not shake the inhaler or spray into the air prior to taking an inhalation
4	Participant shakes the inhaler and then sprays twice into the air in sequence, then shakes the inhaler again and sprays two additional sprays into the air in sequence

Table 8: DMEPA's analysis of participants' failure by subject ID, task, and appropriate mitigation – for Task 1 Initial priming

TASK 1 - Initial priming sequence					
Criteria for failure: moderator assisted, did not shake or spray, did not meet bench study data					
FAILED	Participant ID (b) (6)	Initial priming sequence	Acceptable	Participant ID (b) (6)	Initial priming sequence
20 TOTAL	[redacted]	shook 1x-spray 4-5x >10sec	26	[redacted]	shook 1x, sprayed 4-5x in 10sec
		did not shake, sprayed 3 or less times			shook 1x, sprayed 4-5x in 10sec
		did not shake, sprayed 2x			shook 1x, sprayed 4-5x in 10sec
		did not shake, sprayed 3 or less times			shook 1x, sprayed 4-5x in 10sec
		did not shake or spray			shook 1x, sprayed 4-5x in 10sec
		did not shake or spray			shook 1x, sprayed 4-5x in 10sec
		removed container, shook, replaced, sprayed once			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
		removed container, shook, replaced, sprayed once			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
		did not shake, sprayed 1x or more			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
		did not shake, sprayed 1x or more			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
		did not shake or spray			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
		did not shake or spray			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
		did not shake or spray			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
		did not shake or spray			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
		shook 1x, sprayed <4x in sequence			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
		shook 1x, sprayed <4x in sequence			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
		shook 1x, sprayed <4x in sequence			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
		shook 1x, sprayed <4x in sequence			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
		shook 1x, sprayed <4x in sequence			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
		shook 1x, sprayed <4x in sequence			shook 1x, sprayed 4x in sequence w/out shaking in between sprays
					shook 1x, sprayed 4x in sequence w/out shaking in between sprays
					shook 1x, sprayed 4x in sequence w/out shaking in between sprays
					shook then sprayed 2x, then shook again, then sprayed 2x again
					shook then sprayed 2x, then shook again, then sprayed 2x again
					shook then sprayed 2x, then shook again, then sprayed 2x again
					shook then sprayed 2x, then shook again, then sprayed 2x again

Task 2: Cleaning to Prevent Clogging:
Cleaning procedures requires users to remove the cap and container from the mouthpiece, run water through the body of the mouthpiece for 30 seconds, and then correctly reassemble the inhaler. Applicant conducted additional bench tests which showed if users run water through the body of the mouthpiece for 2 seconds or more, it is sufficient to prevent clogging. Thus, they determined that cleaning the mouthpiece for at least 15 seconds during the simulation was considered a "Completed" task performance.

Statistical analysis results (from Quantitative Analysis Report for Human Factors Study, p.45):

Detailed Items for Human Factors	# of Participants (TEP*)	Study Results				Lower Limit of 95% confidence Interval, %		
		C	CI	NC	Acceptable Rate, %	Exact Method	>85%?	Normal Approximation
Task-2 Performance, Overall	151	91	56	4	97.4%	93.4%	√	94.8%
2a Cleaning by Washing	151	91	56	4	97.4%	93.4%	√	94.8%
1) Twist & pull out container, set aside	151	136	12	3	98.0%	94.3%	√	95.8%
2) Remove cap	151	150	0	1	99.3%	96.4%	√	98.0%
3) Wash either end, running water	151	128	20	3	98.0%	94.3%	√	95.8%
4) Overall Rinse Time	151	95	53	3	98.0%	94.3%	√	95.8%
2b Place container back in mouthpiece	151	145	3	3	98.0%	94.3%	√	95.8%
1) Container placed into inhaler correctly	151	145	3	3	98.0%	94.3%	√	95.8%
2) Fully seated in place	151	145	3	3	98.0%	94.3%	√	95.8%

- Mouthpiece washing time:
  - Average washing time = 20.3+/- 15 sec
  - Median washing time = 18 seconds; with a range of 0 to 120 seconds
  - 147 (97%) washed for more than 2 secs
  - 95 (63%) washed for more than 15 secs
  - 51 (34%) washed for more than 30 secs
- N=4 had scores of not completed (NC) – did not complete task correctly and washed in less than 2 seconds
- N=56 had scores of completed with issues (CI) – did not wash for at least 15 seconds and/or in some way deviated from the instructions

Qualitative data from the Human Factors Engineering Report:
Not Completed (NC) use errors observed with Task 2 – Wash to prevent clogging (N=4):

N	Use Error
3	Participant does not remove the container in order to run water through the mouthpiece body, and does not demonstrate an understanding of the need to wash the inhaler to prevent clogging.
1	Participant does not wash, despite demonstrating an understanding of the need to wash.

Distribution of use issues by user group:

User Group		Not Completed (NC)	Completed with Issues (CI)	Total use issues per user group
Adult – Normal Literacy	Inhaler Experienced	1	5	6
	Inhaler Naive	0	37	37
Adult – Low Literacy	Inhaler Experienced	0	1	1
	Inhaler Naive	1	6	7
Juvenile	Inhaler Experienced	1	5	6
	Inhaler Naive	1	2	3
Total use issues		4	56	60

Root Cause – Lack of awareness of the need to clean the inhaler resulting from a failure to read the instructions for use prior to completing the task

- N=3 had scores of not completed (NC)

Root Cause – Negative knowledge transfer from prior inhaler experience and abnormal use

- N=1 had score of not completed (NC)

Completed with Issues (CI) use errors observed with Task 2 (N=56):

N	Use Error
52	Participant did not clean the inhaler for at least 15 seconds during the initial simulation.
12	Participant did not remove the container before cleaning the inhaler during the initial simulation.

- 56/151 participants (37%) did not clean the inhaler as directed in the instructions during the initial simulation. However, during the course of the test session, these participants either demonstrated the correct cleaning process or they both articulated correct comprehension of critical elements of the cleaning instructions (i.e., to prevent clogging, to be performed routinely, and to ensure that the inhaler expels a full spray in order to deliver a full dose of medication), and they described an adequate strategy for achieving that goal. The majority of these participants performed the task incorrectly initially because they did not rinse the inhaler under running water for at least 15 seconds (52/151, 34% of participants). Some participants (12/151, 8%) did not remove the medicine container during their initial cleaning simulation. Participants may be listed twice if they experienced both kinds of use errors during their initial cleaning simulation.

Table 9: DMEPA's analysis of participants' failure by subject ID, task, and appropriate mitigation – for Task 2 Cleaning the inhaler

TASK 2 - Cleaning the inhaler				
Criteria for failure: washed for less than 2 seconds, did not meet bench study data				
FAILED	Participant	Initial simulation	Acceptable	Initial simulation
18 TOTAL	(b) (6)	did not remove container or demonstrate understanding need to wash	42	these participants did not clean inhaler for at least 15 seconds (b) (6)
		did not remove container or demonstrate understanding need to wash		
		did not remove container or demonstrate understanding need to wash		
		did not wash despite demonstrating understanding need to wash		
		did not remove container before cleaning inhaler		
		did not remove container before cleaning inhaler		
		did not remove container before cleaning inhaler		
		did not remove container before cleaning inhaler		
		did not remove container before cleaning inhaler		
		did not remove container before cleaning inhaler		
		did not remove container before cleaning inhaler	(b) (6) *is Applicant typo, corrected to* (b) (6)	
		did not remove container before cleaning inhaler		
		did not remove container before cleaning inhaler		
		did not remove container before cleaning inhaler		
		did not remove container before cleaning inhaler		
		did not remove container before cleaning inhaler		
		(from biostatistics reviewer - washed for less than 2 sec)		
		(from biostatistics reviewer - washed for less than 2 sec)		

Task 3: Routine use of inhaler:

Participants were asked to imagine that they had not had an asthma attack for a couple of weeks, but were experiencing symptoms again. They were asked to do everything they would need to do, to prepare and use the inhaler. To successfully complete the task, participants were expected to prime the inhaler by shaking it and spraying into the air one time, and then complete the steps necessary to take an inhalation.

Participants were also scored objectively on whether they could demonstrate the correct hand position (i.e., finger in the center of the Dose Indicator) when actuating the inhaler.

Statistical analysis results (from Quantitative Analysis Report for Human Factors Study, p.47):

Detailed Items for Human Factors	# of Participants (TEP*)	Global Results				Lower Limit of 95% confidence Interval, %		
		C	CI	NC	Acceptable Rate, %	Exact Method	>85%?	Normal Approximation
Task-3 Performance, Overall	**151**	**128**	**21**	**2**	**98.7%**	**95.3%**	√	**96.9%**
3a Prime the Device	**151**	**128**	**21**	**2**	**98.7%**	**95.3%**	√	**96.9%**
1) Remove cap	151	151	0	0	100.0%	97.6%	√	100.0%
2) Overall Shake & Spray	151	128	21	2	98.7%	95.3%	√	96.9%
3) Finger on Center	151	150	0	1	99.3%	96.4%	√	98.0%
4) Not in the mouth	151	150	0	1	99.3%	96.4%	√	98.0%
3b Deliver Inhalation	**151**	**150**	**0**	**1**	**99.3%**	**96.4%**	√	**98.0%**
1) Hold inhaler in correct orientation	151	151	0	0	100.0%	97.6%	√	100.0%
2) Squeeze while inhaling	151	151	0	0	100.0%	97.6%	√	100.0%
3) Deep breath/ mouth closed	151	150	0	1	99.3%	96.4%	√	98.0%
3c Post Delivery: Replace cap	**151**	**150**	**0**	**1**	**99.3%**	**96.4%**	√	**98.0%**

- N=2 had scores of not completed (NC) – did not correctly prime during task simulation and did not demonstrate understanding after being referred to IFU

- N=21 had scores of completed with issues (CI) – did not prime inhaler correctly before taking an inhalation self-corrected without prompting or demonstrated understanding and correctly performed task after being referred to IFU

Qualitative data from the Human Factors Engineering Report:

Distribution of use issues by user group:

User Group		Not Completed (NC)	Completed with Issues (CI)	Total use issues per user group
Adult – Normal Literacy	Inhaler Experienced	0	4	4
	Inhaler Naive	0	11	11
Adult – Low Literacy	Inhaler Experienced	1	2	3
	Inhaler Naive	0	4	4
Juvenile	Inhaler Experienced	0	0	0
	Inhaler Naive	1	0	1
Total use issues		2	21	23

For the 2 participants with scores of NC, who never re-primed the inhaler both indicated that they saw and understood the instruction in the Package Insert IFU, but simply would not shake and spray into the air before taking an inhalation. One participant stated this was because he had never done this with any inhalers he had used previously, and the other said she felt it was not important to do it.

Root Cause – Did not read the Package Insert IFU fully before first simulation

Completed with Issues (CI) use errors observed with Task 3 (N=21):

N	Use Error
4	Participant did not initially see the instructions on routine priming in the Package Insert IFU, but then noticed it and independently self-corrected.
8	Participant did not initially see the instructions on routine priming in the Package Insert IFU, but after being referred to the instructions, saw the information about routine priming, demonstrated comprehension, and correctly performed the task.
8	Participant saw the instruction on routine priming in the Package Insert IFU but did not complete the task as directed by the instructions.
1	Participant did not read the Package Insert IFU or carton prior to using the simulations and used the inhaler based upon prior experience with inhalers.

Residual Risk for Task 3:

- The Applicant indicated that they had added language (b) (4) which was done prior to the Validation study, and during the Validation testing, 149/151 (99%) of participants understood this use requirement and were able to demonstrate it correctly.
- Of the two participants (with scores of NC) who failed to re-prime the inhaler, one was a participant who appeared functionally illiterate and who used his prior experience with a dry powder inhaler to guide his usage, and one was a juvenile who read and

understood the instructions in the Package Insert IFU but said that she simply would not follow the instructions because she felt it was not necessary.

Table 10: DMEPA's analysis of participants' failure by subject ID, task, and appropriate mitigation – for Task 3 Routine use

TASK 3 - Routine use					
Criteria for failure: moderator assisted, did not shake or spray, did not meet bench study data					
FAILED	Participant	Initial simulation	Acceptable	Participant	Initial simulation
19 TOTAL	(b) (6)	did not demonstrate proper routine re-priming and use (orig NC)	4	(b) (6)	independantly self-corrected
		did not demonstrate proper routine re-priming and use (orig NC)			independantly self-corrected
		self-corrected after being referred to the instructions			independantly self-corrected
		self-corrected after being referred to the instructions			independantly self-corrected
		self-corrected after being referred to the instructions	(b) (6)	*s Applicant typo, corrected to*	(b) (6)
		self-corrected after being referred to the instructions		*s Applicant typo, corrected to*	
		self-corrected after being referred to the instructions			
		self-corrected after being referred to the instructions			
		self-corrected after being referred to the instructions			
		self-corrected after being referred to the instructions			
		saw instructions on routine priming but did not complete as directed			
		saw instructions on routine priming but did not complete as directed			
		saw instructions on routine priming but did not complete as directed			
		saw instructions on routine priming but did not complete as directed			
		saw instructions on routine priming but did not complete as directed			
		saw instructions on routine priming but did not complete as directed			
		saw instructions on routine priming but did not complete as directed			
		saw instructions on routine priming but did not complete as directed			
		did not read IFU, used inhaler based on prior inhaler experience			

Task 4: Interpreting the dose indicator:
Task 5: Do not rely on dose indicator if inhaler dropped:
Task 6: Correctly hold the inhaler:

Statistical analysis results (from Quantitative Analysis Report for Human Factors Study, p.49):

Detailed Items for Human Factors	# of Participants (TEP*)	Study Results			Lower Limit of 95% confidence Interval, %		
		C	NC	Acceptable Rate, %	Exact Method	>85%?	Normal Approximation
Question-4 Dose Indicator Overall	151	149	2	98.7%	95.3%	√	96.9%
How do you know how many doses are left in your inhaler?	151	149	2	98.7%	95.3%	√	96.9%
How many doses are in your inhaler now?	151	149	2	98.7%	95.3%	√	96.9%
Red zone inhaler	151	149	2	98.7%	95.3%	√	96.9%
What else can you tell me about it?	151	149	2	98.7%	95.3%	√	96.9%
Would not keep tracking inhalations of dose indicator did not move?	151	149	2	98.7%	95.3%	√	96.9%
Question-5 If you dropped device, would not rely on the dose indicator?	151	147	4	97.4%	93.4%	√	94.8%
Question-6 Corectly hold inhaler	151	151	0	100.0%	97.6%	√	100.0%

Task 4: Interpreting the dose indicator:
Evaluated if participants noticed and understood the instructions provided regarding the Dose Indicator, and if they could deploy this understanding to use the inhaler correctly and safely. In particular, participants were evaluated on their understanding of the meaning of the Dose Indicator Red Zone. This task was evaluated through open-ended interview questions. Participants were asked how many doses remained in their inhaler. The moderator then checked the Dose Indicator to determine if the participant answered correctly. Next the participants were given an inhaler that was in the Red Zone and asked how many doses the inhaler held. The moderator recorded if the participant answered correctly or not. In addition, participants were scored objectively on whether or not they could explain, without prompting the following features of the Dose Indicator: a) It does not move with each inhalation; it moves after each 20 uses and b) When in the Red Zone, the inhaler needs to be replaced soon.

- N=2 had scores of not completed (NC) – did not recognize that the inhaler had a Dose Indicator and did not understand how it functioned

Qualitative data from the Human Factors Engineering Report:
Distribution of use issues by user group:

User Group		Not Completed (NC)
Adult – Normal Literacy	Inhaler Experienced	0
	Inhaler Naive	0
Adult – Low Literacy	Inhaler Experienced	2
	Inhaler Naive	0
Juvenile	Inhaler Experienced	0
	Inhaler Naive	0
Total use issues		2

Use errors and root cause:

- For the 2 participants with scores of NC, both were inhaler experiences and performed simulation largely on prior experience. One participant never read or opened the instructions during the simulated use tasks and the other participant appeared functionally illiterate. Both participants did not realize the device had a dose indicator.

Task 5: Do not rely on dose indicator if inhaler dropped:
Evaluated if participants noticed and understood the instructions provided regarding a dropped inhaler, and if they would respond properly in the event that the Dose Indicator should be damaged by dropping the inhaler.
Participants were scored objectively on whether or not they could explain, without prompting not to rely on the dose indicator and to manually keep track of the doses used instead.

- N=4 had scores of not completed (NC) – did not demonstrate appropriate comprehension of the instructions and did not articulate an appropriate approach to dealing with a dropped inhaler

Qualitative data from the Human Factors Engineering Report:
Distribution of use issues by user group:

User Group		Not Completed (NC)
Adult – Normal Literacy	Inhaler Experienced	1
	Inhaler Naive	1
Adult – Low Literacy	Inhaler Experienced	2
	Inhaler Naive	0
Juvenile	Inhaler Experienced	0
	Inhaler Naive	0
Total use issues		2

Use errors:

- Two participants were simply unaware that the device had a Dose Indicator
- Two participants did not express any intention to track their usage should the Dose Indicator fail to work properly

Root Cause Analysis:

- Did not know the inhaler had a Dose Indicator – because did not read IFU completely
    - Performed the simulation tasks based on his prior inhaler experience, did not look at the Package Insert IFU prior to or during his use, then when shown IFU, understood how Dose Indicator works, but never indicated noticed or read instructions on dropped inhaler
    - Participant never found the Dose Indicator during the test session
- The instruction on the Package Insert IFU did not clearly convey the risk of a malfunctioning Dose Indicator – did not anticipate any potential risk of running out of medication unexpectedly based on the instructions provided in the Package Insert IFU

Task 6: Correctly hold the inhaler:

Evaluated if participants understood of the correct finger position required to ensure that the device expels medication properly with each spray.

Participants were scored objectively on whether or not they understood the need to correctly place their finger on the center of the dose indicator.

- 151 (100%) participants demonstrated appropriate comprehension of the correct finger position required

HF Validation Study Moderator's Script

Study Introduction

Thank you for coming in today. We are conducting a study to evaluate a new product for use in the treatment of mild symptoms of asthma. This kind of study is part of a process that is required by the FDA in order to make sure that new medical products are designed in a way that they are safe and that people can use them correctly. Your participation in this study is so important because it is the only way that we make sure that people can use this product safely and that they can understand how to follow the instructions.

This product will not require a prescription from a physician. It will be sold over-the-counter in drug stores and pharmacies and it is intended for use by lay people, that is--people who are not healthcare professionals. It is not something you would use everyday. It is for people who occasionally have mild asthma symptoms. When they have those symptoms, they would use the product and then they would not use it again until they have more asthma symptoms. Do you have any questions about that?

Okay, this is the product we are evaluating today. The carton I am giving you contains a new inhaler and **a package insert with the instructions on how to use the product.** You can take everything out of the carton, look at and handle everything that is inside the carton. You will be able to take as much time as you like to familiarize yourself with these things.

The product that I am giving you today looks and works exactly the way the real product will except that it does not contain any drug product. The product I will give you is filled with a placebo--that means, some inactive ingredients that do not contain any medicine. It is harmless. Once you have had a chance to familiarize yourself with the product and you feel that you are ready, I will ask you to go ahead and use the product. Because it is filled with a placebo, you will feel the mist when you use the product, but remember that there is no drug product in the container. Any questions or concerns?

Our goal today is to understand, from your perspective, whether you are able to use the product safely and effectively, without the assistance of a healthcare provider.

Do you have any questions?

Let's begin. Here is the product. At this point I would like you to do what you would normally do in real life to familiarize yourself with a new medical product. You can open the package and remove contents. Please take as long as you like learning about the product; we have plenty of time. Once you feel comfortable, I will have you actually use it, as if you were using it in real life. Also, this is not a memory test. You can use any of the materials provided with the product, just as you might if you were using the product on your own at home.

[For those with inhaler experience]

It is important that you keep in mind that the inhaler you will use today may work differently than the one you are used to or may have used in the past.

Any questions? Are you ready to get started?

(Moderator will allow the participant to familiarize him/herself with the product without any assistance or interference. The moderator will observe and record the participant's activities. When participant signals he/she is ready to use the product, the Moderator will begin to introduce the simulated use scenarios.)

Retrieved IFU: ▫ Yes ▫ No

Time spent on IFU: _____ Time spent reading the carton: _____

Total Time: _____

General Introduction to Behavioral Scenarios

At this point, I have a few different scenarios that I would like you to try with the product. These are things that you would do if you were using the product for controlling asthma. I'll give you several "scenarios". For each one, it's important that you don't skip any steps just because this is simulation. Do everything you would actually have to do in real life. Keep in mind that if you skip something because you are doing here in our lab, I won't know if that is the reason you skipped a step, or if you didn't know to do it, or if you didn't see the instruction.

I will observe you use the product but I will not be able to answer any questions. However, you can refer to the instructions or the information on the carton at any time. Keep in mind that we are not trying to test your memory. When you are done we will talk about your experience and I will answer any questions you have.

Ready to get started?

Scenario 1 — First Use

Prompt: Now, I would like you to imagine that you have purchased this product at the drugstore and you have had time to familiarize yourself with it, but you have not needed to use it yet and it has never been removed from the box. Today you are feeling some asthma symptoms and you are going to use it for the very first time. Please go ahead and do everything you would need to do to use it for the first time. Take as much time as you need. There is no hurry. The most important thing is that you complete all the necessary steps needed to prepare and use the product correctly.

Scenario 1 — First Use **Overall Task Performance Score:** ▫ C ▫ CI ▫ NC

Step/Sub-Task	Potential Use Issue / Notes
Prime the device ✓ Remove cap ✓ Shake and spray 4x ✓ Finger on center ✓ Not into mouth	▫ C ▫ CI ▫ NC ▫ shake 4x /spray 4x ▫shake 1x /spray 4x ▫ other, _____
Deliver an inhalation ✓ Hold inhaler in correct orientation	▫ C ▫ CI ▫ NC
✓ Squeeze while inhaling ✓ Deep breath	
Replace cap	▫ C ▫ NC
What, if anything, would you do next?	
Other issues/comments: *(Make sure to capture evidence that the participant understands the risk of not priming correctly. For example: they may not get the full dose.)*	

[When the participant is finished, the Moderator will ask:]

Do you think that you completed that task successfully? How do you know?

Is there anything you would do differently if you did the task again?

Okay. We will talk more about your experience using the product in a few minutes. But first I want to ask you to complete a couple more tasks.

Scenario 2 — Cleaning

Prompt: This time I would like you to imagine that you have used your inhaler a couple of times today. Now you have used your inhaler for the last time today and you are getting ready for bed. What would you do with your inhaler before going to bed?

If used, wash mouthpiece with water at night.	▫ wash with water (Correct, *go to cleaning observation*) ▫ It says to wash it, but I wouldn't (Correct--*shows label comprehension; participant must also demonstrate the behavior)* ▫ Nothing/Put it away, etc. (*Probe to determine if response/lack of response is a test artifact and if so, go to Alternative Prompt A)*

Prompt: Okay, now can go ahead and show me how you would clean your inhaler?

Cleaning the Inhaler Overall Task Performance Score: ▫ C ▫ CI ▫ NC

Step/Sub-Task	Potential Use Issue / Notes
Twist and pull out container, set aside	▫ C ▫ CI ▫ NC
Remove the cap	▫ C ▫ CI ▫ NC
Wash either end under running water ✓ 15 seconds	▫ C ▫ CI ▫ NC Document how long _____
What would you do next?	▫ air dry overnight ▫ towel dry and reassemble ▫ reassemble ▫Other, _____
Place container back in mouthpiece *(if applicable)* ✓ container placed into inhaler correctly ✓ fully seated in place	▫ C ▫ CI ▫ NC

(*If participant does not wash under running water or wash for at least 15 seconds, then go to Alternate Prompt A)*	
Other Issues or comments	

[When the participant is finished, the Moderator will ask:]

Do you think that you completed that task successfully? How do you know?

Is there anything you would do differently if you did the task again?

Alternate Prompt A: What if you have been using your inhaler for a while now and it has been working fine. But the last time you used it, or maybe the last couple of times, you noticed that when you take a puff, you feel like you are not getting the same amount of medication. There seems to be less spray coming out. What would you think or do at that point?

Response:	▫ It might be clogged (Go to question 1 below) ▫ Empty or It might be running out or Get a new inhaler (Go to question 2 below) ▫ Other_____ (Go to Alternate Prompt B)
1. What would you do then?	▫ Wash it / Rinse under water (CI, then they have to demonstrate cleaning) ▫ Discard / Get a new one ▫ Other_____ (Go to Alternate Prompt B)
2. Assume the dose indicator reads 120 and you know the dose indicator is working properly and there is medication in the inhaler.	▫ It might be clogged (Go to question 1 above) ▫ Wash it / Rinse under water (CI, then they have to demonstrate cleaning) ▫ Discard / Get a new one ▫ Other_____ (Go to Alternate Prompt B)
Other issues/comments:	

Alternate Prompt B: Does this inhaler ever need to be cleaned?

Response:	▫ Yes (go to question 1 below) ▫ No (Not Correct)
1. When do you think you would you clean it?	▫ Every day after use (go to question 2) ▫ After each use (go to question 2) ▫ Other_____
2. Why do you think you would clean it?	▫ Prevent clogging (CI, then they have to demonstrate cleaning) ▫ Disinfect/clean germs (NC) ▫ Other_____
Capture comments on cleaning in order to prevent clogging:	

After alternative Prompt A or B, if the participant demonstrates correct understanding of the cleaning communication objective, the moderator will have the participant demonstrate cleaning the inhaler.

Scenario 3 — Routine Use of an Already Primed Inhaler

Prompt: I would like to ask you to use your inhaler one more time. You have not had an asthma attack for a couple of weeks, but today you have symptoms again. I want you to complete all the steps necessary to make sure that you use the inhaler properly and that you get a full puff of the medication. Please go ahead. Now remember you are pretending that it's been two weeks since you used this product. We don't expect you to remember everything from one time to the next. You can consult the information provided with the product or on the carton as you complete this task.

Scenario 3 — Routine Use of an Already Primed Inhaler

Overall Task Performance Score: ▫ C ▫ CI ▫ NC

Step/Sub-Task	Potential Use Issue / Notes
Prime the device ✓ Remove cap ✓ Shake and Spray 1x ✓ Finger on center ✓ Not in the mouth	▫ C ▫ CI ▫ NC
Deliver an inhalation ✓ Hold inhaler in correct orientation ✓ Squeeze while inhaling ✓ Deep breath/mouth closed	▫ C ▫ CI ▫ NC
Replace cap	▫ C ▫ NC
Other issues/comments: *(Make sure to capture evidence that the participant understands the risk of not priming correctly. For example: they may not get the full dose.)*	

[When the participant is finished, the Moderator will ask:]

Do you think that you completed that task successfully? How do you know?

Is there anything you would do differently if you did the task again?

Additional Labeling Comprehension (Knowledge Tasks)

Interpreting the Dose Indicator

Overall Comprehension Performance Score: ▫ C ▫ NC

How do you know how many doses are left in your inhaler?

▫ Identifies the Dose Indicator (Correct)

▫ Does not know (Not Correct)

▫ Provides explanation of how the dose indicator works (response captured below)

Can you tell me the number of doses left in your inhaler right now? *(Moderator will verify by checking the dose indicator.)*

- ▫ Correct (C)
- ▫ Not Correct (NC)

(The Moderator will present a second device that has a dose indicator in the Red Zone.)

What about this inhaler. Can you tell me how many doses it has in it?

- ▫ Correct (C)
- ▫ Not Correct (NC)

What else can you tell me about it?	▫ Understands significance of the Red (C) ▫ Does NOT understand the significance of the Red (NC)
Response: *(An overall **Correct** score requires that the participant understands when the inhaler is nearing an empty state.)*	

Can you explain to me how the dose counter works?	▫ It does not move with each inhalation ▫ When it is in the Red Zone, the inhaler needs to be replaced soon
Response:	

What would you think if you had used your inhaler, but you do not see the dose indicator change? (Moderator--If participant says broken, Moderator Response: "Assume it is not broken.")	▫ Nothing, it moves after 20 uses (Correct) ▫ The device / indicator is broken (Not Correct) ▫ Other
Response:	

Would you do anything else at that point? ▫ Would NOT continue dosing *(Correct; This response is required for an overall **Correct** score. Moderator will capture response to provide detail below as needed.)* ▫ Would continue dosing (Not Correct) Response:

Do Not Rely on the Dose Indicator if the Device is Dropped

Overall Comprehension Performance Score: ▫ C ▫ NC

If you dropped the device what, if anything, would you do? Would you do anything different with the dose indicator?	▫ Would NOT rely on the dose indicator; would keep track of doses used instead [Correct (C)] ▫ Nothing different [Incorrect (NC)] ▫ Other _____
*A **Correct** overall score requires that the moderator documents a participant responses that indicates the participant understands the risk that the dose indicator may not be accurate and would take appropriate action to ensure they don't keep using an empty/nearly empty inhaler.*	
Response:	

Holding the Inhaler Properly to Administer an Inhalation

Overall Comprehension Performance Score: ▫ C ▫ NC

Can you show me again how you hold the inhaler when you are giving yourself a puff? Why do you do that?	▫ Finger in center of dose indicator [Correct (C)] ▫ Does not understand (NC), describe:
*A **Correct** overall score requires that the moderator documents a participant response the indicates the participant understands the risk of pressing on the side/edge of the container (i.e., that they will not get a correct dose or a full spray, etc.).*	
Response:	

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On October 26, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Newsletter Community Newsletter Nursing Newsletter
Search Strategy and Terms	Match Exact Word or Phrase: Primatene

D.2 Results

Our search did not retrieve any results.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on October 26, 2016 using the criteria below, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[f]

FAERS Search Strategy	
Initial FDA Receive Dates	**1/1/2000 to 10/1/2016**
Product Name	**Primatene Mist**
Event (MedDRA Terms)	*Medication errors* SMQ (narrow)

E.2 Results

Our search identified 34 cases, but after further evaluation, we did not identify any medication error cases that were relevant for this review and that could be addressed by labels and labeling revisions.

E.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[f] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following (b) (4) labels and labeling submitted by Armstrong Pharmaceuticals, Inc. on 6/28/2016.

- Instructions for Use
- Carton Labeling
- Container Label

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

GRACE JONES
12/06/2016

DANIELLE M HARRIS
12/06/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, Ophthalmic

Date: November 30, 2016

To: Thao Vu, Office of Pharmaceutical Quality, WO75- 4509
thao.vu@fda.hhs.gov

Danae Christodoulou, Office of Pharmaceutical Quality, WO21-2602
danae.christodoulou@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Thao Vu

Through: Francisco Vicenty, Chief, REGO, DMQ, OC, CDRH

Francisco Vicenty -S
2016.11.30 14:30:25 -05'00'

From: Jamie Kamon-Brancazio, REGO, DMQ, OC, CDRH

Applicant: Armstrong Pharmaceuticals, Inc.
25 John Road
Canton, Massachusetts 02021
FEI# 3007009553

Application # NDA-205920

Consult # ICC1600464

Product Name: Epinepherine

Combination Product Intended Use: Temporary relief of mild symptoms of intermittent asthma

Pre-Approval Inspection: No

Documentation Review: Additional Information Required

Final Recommendation: **Approve; Recommended Inspectional Guidance for next Routine inspection**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA-205920.

PRODUCT DESCRIPTION

Armstrong's (b) (4) is a non-prescription drug product indicated as a rescue inhaler for temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. The proposed Product, Epinephrine Inhalation Aerosol USP, an HFA-MDI, as a neutral HFA suspension, will be supplied with (b) (4) 160 metered inhalation doses in aluminum aerosol canister with metered valve assembled to an actuator.

(b) (4)

REGULATORY HISTORY

The following facility was identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

Armstrong Pharmaceuticals, Inc.
25 John Road
Canton, Massachusetts 02021
FEI# 3007009553

Responsibility – Applicant- Drug Product Manufacturer: Raw material and component receiving, testing and release, compounding, filling, labeling, packaging, in-process testing, finished product testing, stability testing, storage and distribution.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on March 31- April 3, 2014. The inspection covered Drug GMP requirements and was classified NAI. This was a pre-approval inspection for this NDA.

Inspection Recommendation:

An inspection is not required because:

- A recent Drug GMP inspection of the firm was acceptable.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product, therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance on page# 9).

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

(b) (4)

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(b) (4)

Documentation Review Recommendation

This application was deficient overall. Additional information is required for an adequate documentation review.

Deficiencies to be conveyed to the applicant

The following documentation deficiencies related to NDA-205920 were identified in reference to 21 CFR Part 4 and 21 CFR 820 for the finished combination product, (b) (4) should be sent to the Applicant/Licensure of the Application.

(b) (4)

Please be noted that combination products manufactured under the CGMP drug operating system, the Applicant/Licensure must also fulfill the requirements under 21 CFR Part 4.4b to show compliance to 21 CFR Part 4 for the finished combination product. To assist in the preparation of the above summaries related to the 21 CFR 820.20, 21 CFR 820.30, 21 CFR 820.50 and 21 CFR 820.100, you are recommended the FDA Guidance 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003) located at the link:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

RECOMMENDATION

CDRH OC recommends approval of the application for (b) (4) -NDA-205920. Inspectional guidance was drafted to verify Part 4 compliance during the next routine inspection.

Jamie Kamon-brancazio -S

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DN c=US o=U.S. Government ou=HHS ou=FDA ou=People 0.9.2342.19200300.100.1.1=2001568505 cn=Jamie Kamon brancazio -S
Date: 2016.11.30 14:33:34 -05'00'

Jamie Kamon-Brancazio

Prepared: Kamon-Brancazio: 11/30/16
Reviewed: FMLast name: Month/Day/Year

CTS No.: ICC1600464
NDA-205920

Review Cycle Meeting Attendance:
Month/Day/Year
Month/Day/Year
Month/Day/Year

Inspectional Guidance

Firm to be inspected:
Armstrong Pharmaceuticals, Inc.
25 John Road
Canton, Massachusetts 02021
FEI# 3007009553

CDRH recommends the inspection under the applicable Medical Device Regulations of Armstrong Pharmaceuticals, Inc., located in Canton, USA (FEI # 3007009553).

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Jamie Kamon-Brancazio
CSO,
REGO,
DMQ
Office of Compliance, WO66 RM 3427
Phone: 301-796-3187

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Francisco Vicenty
Branch Chief,
REGO,
DMQ
Office of Compliance, WO66 RM 3426
Phone: 301-796-5577

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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/s/

THAO M VU
12/01/2016
upload on behalf of CDRH

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, Ophthalmic

Date:	December 1, 2016
To:	Thao Vu, Office of Pharmaceutical Quality, WO75- 4509 thao.vu@fda.hhs.gov Danae Christodoulou, Office of Pharmaceutical Quality, WO21-2602 danae.christodoulou@fda.hhs.gov Office of combination products at combination@fda.gov **RPM:** Thao Vu
From:	Francisco Vicenty, Chief, REGO, DMQ, OC, CDRH
Applicant:	Armstrong Pharmaceuticals, Inc. 25 John Road Canton, Massachusetts 02021 FEI# 3007009553
Application #	NDA-205920
Consult #	ICC1600464
Product Name:	Epinepherine
Combination Product Intended Use:	Temporary relief of mild symptoms of intermittent asthma
Subject:	**Addendum to NDA-205920_ICC1600464 Review Memo**

The purpose of this addendum is to clarify the expectations of the NDA-205920 Review memorandum.

REGULATORY HISTORY

The following facility was identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

Armstrong Pharmaceuticals, Inc.
25 John Road
Canton, Massachusetts 02021
FEI# 3007009553

Responsibility – Applicant- Drug Product Manufacturer: Raw material and component receiving, testing and release, compounding, filling, labeling, packaging, in-process testing, finished product testing, stability testing, storage and distribution.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on March 31- April 3, 2014. The inspection covered Drug GMP requirements and was classified NAI. This was a pre-approval inspection for this NDA.

Inspection Recommendation:

A preapproval inspection is not required because as the recent Drug GMP inspection of the firm covered elements that demonstrated compliance of the facility and the device. The inspection results were found to be was acceptable and provided an adequate demonstration of GMP compliance.

DOCUMENTATION REVIEW

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

Documentation Review Recommendation
Additional information is required for an adequate documentation review. This information should be collected during a post-approval inspection.

RECOMMENDATION
The applicant has a demonstrated GMP compliance and there is low manufacturing risk for the device constituent. This device has been previously manufactured by the applicant and the only modification to the process was a change to the propellant used to meet current environmental requirements. Given the assessment, CDRH OC recommends approval of the application for (b) (4) -NDA-205920. Inspectional guidance was drafted to verify Part 4 compliance during a post-approval inspection. This post-approval inspection should be scheduled as part of the approval.

Francisco Vicenty -S
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_____
Francisco Vicenty

Prepared: Francisco Vicenty 12/1/2016

CTS No.: ICC1600464
NDA-205920

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/s/

THAO M VU
12/01/2016
upload on behalf of CDRH

FDA Social Science Review: Consumer Studies

Division of Nonprescription Drug Development

Date:	November 2, 2016
From:	Barbara Cohen, MPA, Social Scientist, DNDP
Through:	Frank Becker, MD, Clinical Team Leader, DNDP
To:	Theresa Michele, MD, Director, DNDP
Subject:	Label comprehension studies supporting the over-the-counter (OTC) approval for epinephrine inhalation aerosol hydrofluoroalkane at a dose of 12.5 mcg/actuation for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older.

TABLE OF CONTENTS

1. Executive Summary

The Applicant conducted three label comprehension studies (LCS) in support of the resubmission of NDA 205920. None of the studies was able to demonstrate that low literacy subjects had good comprehension of all of the circumstances under which they needed to prime the product prior to use.

The three label comprehension studies in the NDA re-submission are the subject of this review. However, subsequent to conducting the studies, the Applicant significantly revised the Instructions for Use (IFU) to simplify and clarify the priming instructions as well as other aspects of labeling. Of most relevance as to whether there is utility of the LCS in informing approval, (b) (4) The revised labeling was streamlined to introduce simplicity and clarity in the IFU. (b) (4) the labeling simply states (b) (4) Assuming that these revised instructions reflect a documented safe and effective use of the product, I commend the Applicant in attempting these revisions.

The revised labeling was then tested in human factors studies, which were fielded approximately a year after the final LCS. The human factors studies are being reviewed separately. The Applicant also simultaneously conducted bench testing that further refined its benefit/risk analysis relevant to LCS and human factors findings. The bench studies are being reviewed separately.

In any considerations for approval, the human factors findings are more directly relevant than the LCS, given the significant changes to the label post LCS. The bench studies are also more relevant for approval as they provide context for the Applicant's benefit/risk assumptions. Nonetheless, I offer a few labeling recommendations for consideration based on the general discussion and assumptions in the submission.

2. Background

Previous Submission and Complete Response

The Applicant originally submitted NDA 205920, a 505(b)(2) new drug application for a reformulation of Primatene Mist, on July 22, 2013. Three label comprehension studies (I, II, III) and one human factors study were included in the NDA (see social science review of April 23, 2014). The application was also discussed at a joint meeting of the Nonprescription Drugs Advisory Committee (NDAC) and the Pulmonary Allergy Drugs Advisory Committee (PADAC) on February 25, 2014, where FDA (DPARP) presented its concerns about the device performance, given the relatively high number of device malfunctions and dose indicator errors reported in the clinical studies.

Following the submission of additional analyses of device and dose indicator performance, FDA sent a Complete Response to the Applicant on May 22, 2014. Along with deficiencies in cGMP and data supporting the safety of chronic inhalation of thymol, the letter cited the high number of device malfunctions in the clinical trials, including apparent user errors with the dose indicators and also with clogging. The results from the label comprehension and human factors study supported these usability issues, in that there were limitations in consumers' understanding of critical information such as: not relying on the dosing indicator if dropped; the need to prime the indicator before using the first time; the need to clean the product daily after use; the need to reprime when wet.

In the CR letter, FDA stated that the Applicant should: *Revise the labeling to optimize comprehension and assess the revised label in a label comprehension study. Optimize the labeling to improve comprehension of the following critical information: prime before first use of the product, clean the product on each day of use, reprime the inhaler when wet, do not rely on the dose indicator if dropped, instructions on removing the canister for cleaning and proper reassembly, press on the center of the dose indicator, and orientation of the product during use and storage.* FDA also advised the Applicant to conduct a human factors study with the revised labeling, including sufficient numbers of low literacy subjects. Additionally, FDA stated that: *Depending on the results of the above iterative evaluations, modification of the product and product labeling may be necessary to minimize potential use error, e.g. revised patient instructions for use, replacement of the current dose indicator with an integrated dose counter, product reformulation and product change to simplify the steps required for adequate product performance, etc.*

Finally, FDA stated that an actual use study should be conducted with the revised labeling to rigorously quantify and evaluate complaints or errors associated with the product and characterize sources of user error.

Resubmission of NDA

On June 28, 2016, the Applicant resubmitted NDA 205290, with three additional quantitative label comprehension studies (IV,V, VI). These three studies are the focus of this review.

Below are the dates that the label comprehension studies were conducted:

Summary of Study Dates for E004 LCS IV, V, and VI

Study	LCS IV	LCS V	LCS VI
Study start date	7/7/2014	9/23/2014	12/9/2014
Study completion date	7/10/2014	10/9/2014	12/11/2014

This NDA is somewhat atypical in that there were significant revisions to the Instructions for Use (IFU) that were implemented *after* the final label comprehension study was completed. This represents best practice and I commend the Applicant for this, particularly given the less than optimal LCS low literacy results. However, it also means that there is extremely limited utility of the LCS alone in informing an approval decision. Instead, the human factors study, which encompassed revised labeling, should serve as the focal point for decision-making relevant to consumer understanding and behavior.

The Human Factors Engineering Report (G3) is cited in this review because it contains a more transparent discussion (than the LCS study reports themselves) about the problems with the IFU that were reflected in the LCS findings. The G3 report, prepared by the human factors contractor and not the LCS contractor, discusses the LCS studies because they were the prelude to the follow-on human factors research. It also discusses the identification and mitigation of use related hazards, which is relevant to the LCS analysis. Therefore, I have drawn on both the LCS study reports as well as a few sections of the G3 report for this review.

3. Label Comprehension Study IV

Design and Conduct

In response to key findings from LCS III, the Applicant determined that product insert changes were needed and that these would be the focus of LCS IV. The changes included:

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

LCS IV was a single-visit study designed to address comprehension of the following primary

objectives:

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

The Applicant states (page 10 of the LCS IV Study Report) that all primary communication objectives were designated as primary endpoints of significant risk based on comments received on May 22, 2014 from the FDA, and were thus assigned a target performance threshold of 85% in keeping with previous label comprehension work conducted.

In addition, the following secondary objective was assessed:

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

This secondary objective was assessed at a 75% threshold and categorized as a secondary objective because, as the Applicant states on page 11 of the LCS IV Study Report, although it was initially theorized in the first NDA submission that the risk of damage to the dose indicator if dropped was high, it turned out that as a result of exhaustive drop tests conducted (study number QAPO-006-14-00-FR), the dose counter never had any critical malfunction.

(Social Science Note: It's unclear then why the currently proposed Instructions for Use (IFU) (b) (4)

Regarding the important objective of "Prime Before First Use," the Applicant asserts that this objective was ultimately deleted from the study during the development of the data collection instrument (page 16). The Applicant asserts that it determined at the time that this objective would be most appropriately addressed in a human factors study setting. *(Social Science Note: the Applicant apparently subsequently changed its mind and decided to assess this primary objective in LCS V)*

The study was conducted in seven mall sites: Chicago IL; Silverdale, WA; Baltimore, MD; Tampa, FL; Lawrenceville, GA; Santa Ana, CA; Lakewood, CO. Potential participants were approached by the study team and asked if they would be willing to participate in a short interview. Consumers under age 16 were excluded, and there were standard exclusion criteria regarding employment, previous study participation and visual acuity. Eligible participants were

brought to an interviewing room, where the REALM was administered to participants 18 years and older, and the REALM-Teen was administered to participants age 16-17. The participants were then given the IFU and asked to read it, taking as much time as they required. Participants were told that they would be asked questions about the information and that they could refer to the insert to answer the questions. Following the comprehension questions, participants were asked about demographics, including whether they suffered from asthma and whether they had ever used Primatene Mist to treat it. The interviewer then asked follow up questions about any comprehension questions that were answered incorrectly. According to the Applicant, the definitions of correct and acceptable responses were pre-specified prior to the conduct of the study, and were contained in the answer key of the questionnaire. However, the scoring also took into account both the responses to structured questions as well as respondents' open ended responses explaining their answers.

The planned sample size was approximately 470, with approximately 118 consumers (25%) who were low literacy. A decision was made to exceed the initial 470 sample in order to ensure that there were sufficient lower literacy participants and account for any missing data. Therefore, a total of 506 completed interviews took place. Table 1 displays the demographics for the sample. Of note, the sample had good Hispanic representation at 14%, as well as fairly good low literacy representation at 25%. Approximately 14% of the sample reported suffering from asthma, with a slightly higher proportion among low literacy than normal literacy participants. The Primatene Mist user cohort included only 36 participants (7%) but demographic characteristics were not significantly different than the non-user cohort.

Table 1: LCS IV Demographics by Literacy

Demographic Characteristics for Subjects by Literacy*
(Survey Population)

Responses	All Combined (N=506)	Normal Literacy [1] (N=379)	Low Literacy [2] (N=126)
Gender			
Male	230 (45%)	175 (46%)	55 (44%)
Female	276 (55%)	204 (54%)	71 (56%)
Race			
White	279 (55%)	224 (59%)	54 (43%)
Black or African American	111 (22%)	74 (20%)	37 (29%)
Hispanic	73 (14%)	49 (13%)	24 (19%)
Asian	6 (1%)	5 (1%)	1 (1%)
Native Hawaiian or Other Pacific Islander	1 (0%)	0 (0%)	1 (1%)
American Indian or Alaska Native	3 (1%)	2 (1%)	1 (1%)
Refused	2 (0%)	2 (1%)	0 (0%)
Other	31 (6%)	23 (6%)	8 (6%)
Education Level			
8th grade or less	3 (1%)	1 (0%)	2 (2%)
Some high school	64 (13%)	28 (7%)	35 (28%)
High school graduate, GED, or certificate	140 (28%)	90 (24%)	50 (40%)
Some college or technical school	180 (36%)	151 (40%)	29 (23%)
College graduate	96 (19%)	88 (23%)	8 (6%)
Post-graduate degree	23 (5%)	21 (6%)	2 (2%)
Age Group Category			
16 - 17	42 (8%)	20 (5%)	22 (17%)
18 - 34	215 (42%)	157 (41%)	58 (46%)
35 - 44	71 (14%)	57 (15%)	14 (11%)
45 - 54	87 (17%)	64 (17%)	23 (18%)
55 - 64	60 (12%)	54 (14%)	6 (5%)
>=65	31 (6%)	27 (7%)	3 (2%)

Demographic Characteristics for Subjects by Literacy*
(Survey Population)

Responses	All Combined (N=506)	Normal Literacy [1] (N=379)	Low Literacy [2] (N=126)
Range	16 - 83	16 - 83	16 - 79
Asthma Sufferer			
Yes	70 (14%)	47 (12%)	23 (18%)
No	433 (86%)	330 (87%)	102 (81%)
Don't know	3 (1%)	2 (1%)	1 (1%)
Primatene Mist User			
Yes	36 (7%)	28 (7%)	8 (6%)
No	469 (93%)	351 (93%)	117 (93%)
Missing	1 (0%)	0 (0%)	1 (1%)

Source: LCS IV Study Report, NDA submission

Applicant-Reported Findings

As Table 2 illustrates, the normal literacy (NL) population achieved high levels of comprehension for most communication objectives. And for the low literacy (LL) population, comprehension of the need to wash the inhaler daily when using it was 91%, with 85% lower bound (LB).

However, low literacy comprehension of "Prime the inhaler again if it is wet, dropped, or not used for more than two days" was 81% for wet (LB of 73%) and 65% for wet, dropped, or not used for more than two days (LB of 56%). The G3 Engineering Report acknowledges on page 70 that these LCS results indicated low comprehension percentages for the low literacy participants.

These findings are of concern because if the product is not primed, it may not work effectively. As the G3 Engineering Report states, "*during the priming process, shaking of the inhaler ensures that the medication is evenly mixed and distributed throughout the canister. If the step is not performed (neither shaking nor spraying), it could create an uneven distribution of the medication and ingredients during the subsequent actuation, such that the product may not provide a full dose during the inhalation. If the user does not perform priming a total of four times, the subsequent uses of the product may not provide full doses during the inhalation.*"

While it is generally assumed by reviewers, medical professionals, and researchers that low literacy consumers may or may not have the same levels of comprehension as normal literacy consumers for a given communications objective – and therefore they might not be expected as a subgroup to meet certain overall study general population thresholds - the ability of low literacy consumers to understand certain aspects of labeling is particularly important for certain products. In the case of Primatene, it would be the only NDA approved nonprescription asthma rescue inhaler. In an August 8, 2011 correspondence with FDA, the Applicant stated "*while recognizing that many inhalation treatment choices are available to physicians treating asthma patients, this product serves a unique and vital role in providing the OTC needs of this patient population. The product serves not only those asthma patients who fail to make their prescribed inhalers available when needed (e.g., prescription is unavailable due to travel), but also those who rely heavily on OTC medications for asthma treatments due to socioeconomic reasons such as lack of health insurance, etc.*" Furthermore, the G3 Engineering Report states on page 12 that the labeling has been designed and iteratively tested to accommodate adult users, juvenile users, and low literacy adults. Importantly, page 15 states that there is no expectation that users of the product will be under the care of a healthcare professional for their intermittent asthma.

While low literacy is not precisely correlated with low socioeconomic demographics, the ability of those of relatively limited literacy to adequately understand the label appears to this reviewer to be particularly important in the case of this product, particularly when considering its potentially life-saving indication and the fact that the Applicant does not expect its users to be under the care of a physician.

The communications objective of “Place your finger on the center of the dose indicator” achieved a low literacy comprehension score of 84%, with a 77% LB. This was not assessed again in LCS but was assessed in the follow on human factors studies. The concern about finger placement arose because, as the G3 Engineering Report discusses, if the user’s finger is offset, the canister could be pushed sideways and not directly downward; the tilting to the side could release additional medication through the valve stem, resulting in less medication remaining in the canister than accounted for in the dose indicator. Should the user continue to use the inhaler towards the end of its life, the dose indicator could show actuations left when there is no medication left in the canister.

Finally, “do not rely on the dose indicator if dropped” had a low literacy comprehension score of 85%, with a LB threshold of 77%. Since the Applicant determined that this was a secondary objective, this objective was not tested again in LCS V and VI. The Applicant asserts that it subsequently determined through bench testing that this was a low risk issue. I defer to other reviewers on this question.

Former Primatene users directionally performed worse on most questions than non-users. However, the cohort for users was very small – only 36 participants, vs 469 non users. Therefore, it’s not possible to draw any conclusions about this. Former users seemed to struggle the most with the concept of priming. Since former Primatene users also tended to be low literate more so than non users, this could have been a factor in the results.

Table 2: LCS IV Applicant Reported Findings

Primary Communication Objectives	Question # and Text	Normal Literacy (95% CI) N = 379	Low Literacy (95% CI) N = 126	Users (95% CI) N = 36	Non-Users (95% CI) N = 469	Asthma Sufferers (95% CI) N = 70	Non-Asthma Sufferers (95% CI) N = 436	Total (95% CI) N = 506
1. Wash the mouthpiece daily if used	Question 6: *According to the package insert, how often should the mouthpiece be washed?*	97% (94%, 98%)	91% (85%, 96%)	94% (81%, 99%)	95% (93%, 97%)	94% (86%, 98%)	95% (93%, 97%)	95% (93%, 97%)
2. Prime the inhaler again if it is wet, dropped, or not used for 2 days	Question 8: *John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do?*	90% (87%, 93%)	81% (73%, 87%)	81% (64%, 92%)	88% (85%, 91%)	84% (74%, 92%)	88% (85%, 91%)	88% (85%, 90%)
	Question 4: *You must prime the inhaler before you first use it. When else do you have to prime the inhaler again?*	89% (85%, 92%)	65% (56%, 73%)	78% (61%, 90%)	83% (79%, 86%)	80% (69%, 89%)	83% (79%, 86%)	83% (79%, 86%)
3. Place finger(s) on center of dose indicator	Question 5: *Mike needs to take an inhalation to treat his asthma attack. To properly take an inhalation or puff, where should he place his finger?*	91% (88%, 94%)	84% (77%, 90%)	94% (81%, 99%)	89% (86%, 92%)	83% (72%, 91%)	90% (87%, 93%)	89% (86%, 92%)
4. Instructions for removing the canister for cleaning mouthpiece	Question 7: *Susie needs to wash her inhaler. What is the first step she must take?*	97% (94%, 98%)	94% (88%, 97%)	100% (90%, 100%)	95% (93%, 97%)	96% (88%, 99%)	96% (93%, 97%)	96% (93%, 97%)
5. Children under 12 years of age: do not use	Question 1: *Meghan has a 6-year old son who has asthma. What, if anything, does the insert say about giving this medicine to her son?*	98% (96%, 99%)	93% (87%, 97%)	94% (81%, 99%)	97% (95%, 98%)	97% (90%, 100%)	97% (94%, 98%)	97% (95%, 98%)
6. Do not use more than 8 inhalations in 24 hours	Question 2: *Bill has taken 8 inhalations of Primatene® HFA today, but is still having asthma symptoms. Is it okay for him to use more Primatene® today?*	93% (90%, 95%)	89% (82%, 94%)	94% (81%, 99%)	91% (89%, 94%)	86% (75%, 93%)	93% (90%, 95%)	92% (89%, 94%)
7. See your doctor if you have more than 2 asthma attacks in a week	Question 3: *Camille has had 4 asthma attacks in one week. According to the insert, what should Camille do?*	99% (98%, 100%)	95% (90%, 98%)	100% (90%, 100%)	98% (96%, 99%)	97% (90%, 100%)	98% (96%, 99%)	98% (96%, 99%)

Source: Narrative Response to the Statistical Information Request dated September 6, 2016

Secondary Communication Objective	Question # and Text	Normal Literacy (95% CI) N=379	Low Literacy (95% CI N=126	Users (95% CI) N=36	Non-Users (95%CI) N=469	Total (95% CI) N=506
1. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take	**Question 9:** *Based on the package insert, what should you do if you drop your inhaler?*	98% (96%, 99%)	85% (77%, 91%)	94% (81%, 99%)	94% (92%, 96%)	94% (92%, 96%)

Source: LCS IV Study Report, NDA submission

Finally, it should be noted that although FDA did not request this in the Complete Response, the Applicant decided to assess comprehension of "Children under age 12, do not use", "Do not use more than 8 inhalations in 24 hours", and "see your doctor if you have more than two asthma attacks in one week". The Applicant states that it undertook this assessment as a result of feedback from several Advisory Committee members during the 2014 meeting. While the comprehension scores for "see your doctor if you have more than two asthma attacks in one week" were excellent among low literacy as well as normal literacy respondents, and the comprehension scores for "under 12 do not use" were excellent among normal literacy and 93% for low literacy (87% LB), the comprehension scores for "do not use more than 8 inhalations in 24 hours" were very good for normal literacy but 89% for low literacy, with a 82% LB. This statement may need to be additionally highlighted on the DFL, which would also reinforce the concept that the indication is for mild symptoms of intermittent asthma only.

4. Label Comprehension Study V

Design and Conduct

According to the LCS summary contained in the Human Factors G3 Engineering Report (page 72 of 198), based on these and other results, it was determined that product insert design changes were needed and that this would be the result of Study V. (*Social Science Note: the report did not elaborate on what the other results were.)*

The changes included:

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

LCS V was conducted in five mall sites: Chicago IL; St Paul, MN, Bensalem, PA, Roseville, CA, and Vancouver, WA.

The planned sample size was approximately 470, with approximately 118 consumers (25%)

who were low literacy. A decision was made to exceed the initial 470 sample in order to ensure that there were sufficient lower literacy participants and account for any missing data. Therefore, a total of 492 completed interviews took place. Table 3 displays the demographics for the sample. Of note, the sample had poor Hispanic representation at 6%, as well as slightly lower low literacy representation than LCS IV, at 23%. Approximately 18% of the sample reported suffering from asthma, with a slightly higher proportion among low literacy than normal literacy participants. The Primatene Mist user cohort included only 25 participants (5%) but demographic characteristics were not significantly different from the non-user cohort.

Table 3: LCS V Demographics by Literacy

Demographic Characteristics for Subjects by Literacy
(Survey Population)

Responses	All Combined (N=492)	Normal Literacy [1] (N=379)	Low Literacy [2] (N=113)
Gender			
Male	232 (47%)	173 (46%)	59 (52%)
Female	260 (53%)	206 (54%)	54 (48%)
Race			
White	312 (63%)	260 (69%)	52 (46%)
Black or African American	101 (21%)	67 (18%)	34 (30%)
Hispanic	30 (6%)	19 (5%)	11 (10%)
Asian	15 (3%)	9 (2%)	6 (5%)
Native Hawaiian or Other Pacific Islander	5 (1%)	2 (1%)	3 (3%)
American Indian or Alaska Native	6 (1%)	3 (1%)	3 (3%)
Other	23 (5%)	19 (5%)	4 (4%)
Education Level			
8th grade or less	1 (0%)	1 (0%)	0 (0%)
Some high school	66 (13%)	38 (10%)	28 (25%)
High school graduate, GED, or certificate	190 (39%)	138 (36%)	52 (46%)
Some college or technical school	172 (35%)	142 (37%)	30 (27%)
College graduate	51 (10%)	48 (13%)	3 (3%)
Post-graduate degree	12 (2%)	12 (3%)	0 (0%)
Age Group Category			
16 - 17	37 (8%)	23 (6%)	14 (12%)
18 - 34	276 (56%)	215 (57%)	61 (54%)
35 - 44	52 (11%)	40 (11%)	12 (11%)
45 - 54	52 (11%)	37 (10%)	15 (13%)
55 - 64	42 (9%)	35 (9%)	7 (6%)
>=65	33 (7%)	29 (8%)	4 (4%)

Demographic Characteristics for Subjects by Literacy*
(Survey Population)

Responses	All Combined (N=506)	Normal Literacy [1] (N=379)	Low Literacy [2] (N=126)
Range	16 - 83	16 - 83	16 - 79
Asthma Sufferer			
Yes	70 (14%)	47 (12%)	23 (18%)
No	433 (86%)	330 (87%)	102 (81%)
Don't know	3 (1%)	2 (1%)	1 (1%)
Primatene Mist User			
Yes	36 (7%)	28 (7%)	8 (6%)
No	469 (93%)	351 (93%)	117 (93%)
Missing	1 (0%)	0 (0%)	1 (1%)

Source: LCS Study Report V, NDA submission

LCS V was a single-visit study designed to address comprehension of the following primary objectives:

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

As in LCS IV, all primary communication objectives were designated as primary endpoints of significant risk based on comments received on May 22, 2014 from the FDA, and were thus assigned a target performance threshold of 85% in keeping with previous label comprehension work conducted.

The Applicant states in the Response to Information Request dated 9/9/16 that although it had intended on only evaluating priming before first use in the behavior study, it then decided to assess this in LCS V "to provide additional supporting evidence for this objective."

In the Response to Information Request dated 9/9/16 as to the detailed clinical rationale for the 85% threshold, the Applicant has provided detailed clinical justifications for the target threshold relative to priming before first use. The Applicant states that this performance target was determined to be appropriate given the minor clinical risk of not receiving a full dose of medication for the first few doses as a result of failing to understand this instruction. The

Applicant states that multiple priming (i.e., four times) of the inhaler is required only for the initial user of the inhaler. Failure to perform the initial priming results in insufficient drug delivery for only the first few uses; subsequent sprays are not impacted because after the first few uses, the inhaler is sufficiently primed.

The Applicant goes on to state further that the DFL instructs users to "see a doctor if you are not better in 20 minutes" This warning instructs consumers to seek medical attention if their asthma symptoms are not relieved (including in the event of insufficient drug delivery), which is important given the product indication of occasional use for "**temporary relief of mild symptoms of intermittent asthma).** (bolding is Applicant's). The Applicant states that "in conclusion, due to the low frequency of failing to initially prime, impacting only the first few uses, as well as the minor clinical consequences mitigated by the warning on the Drug Facts Label, it was determined that the target threshold of 85% was clinically appropriate."

The Applicant's rationale is not clear for two reasons. First, it uses the term "priming" without parsing it for the two separate steps of shaking and spraying. In the LCS, the Applicant did not assess comprehension of what "priming" meant. Therefore, the Applicant seems to be implying in the discussion of LCS results that whether a consumer only shakes, or only sprays, or only shakes and sprays once for initial priming, such actions are equivalent in that they would only impact the first few uses and afterwards dosing would be correct. In fact, my review of five of the human factors videotapes showed that subjects did not always shake *and* spray, even with the revised IFU.

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

Regarding the low literacy score of 75% for priming before first use, the Applicant states in the Response to IR that "*Armstrong does not believe that this result (ie, 75% comprehension) is a true representation of the low literacy population's comprehension of this objective because low literacy subjects were able to successfully demonstrate the behavior of priming the inhaler before first use in study G3. The Applicant believes that the lower scores observed for the low literacy participants on this issue were largely due to the vagueness required of the question asked, which was intended to ensure that the participant was not 'led' to provide a correct answer. Question 1 (regarding prime before first use) from the LCS was as follows: 'Brenda just purchased* (b) (4) *What does she need to do to get a new inhaler ready to use?' "*

I agree that the question in the study was problematic and poorly worded. However, it's unclear the question couldn't be reworded to simply read: "*Brenda just bought Primatene and hasn't used it yet. She is having an asthma attack and is about to give herself a dose of Primatene. What does she need to do first?"*

Applicant-Reported Findings

As Table 4 illustrates, the normal literacy population achieved good comprehension for "prime before first use" (92%, 89% LB) and "place finger on center of dose indicator". (93%, 90% LB), Additionally, "prime when wet" scored at 89% with a 85% LB. "Prime if not used for two days" scored 87%, with a 83% LB. This latter score for the NL population signals difficulties with the label complexity.

The LL population performed poorly, with scores of 75%, 75% and 69% respectively for the priming objectives of prime initially, prime when wet, prime if not used for more than two days. The LB was in the 60-70% percentile for all priming objectives. Moreover, as in LCS IV, "place finger on the center of the dose indicator" did not do exceedingly well, achieving a score of 86%, with a 78% LB. The G3 Engineering Report acknowledges on page 74 that the results showed low comprehension percentages for low literacy participants.

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

Table 4: LCS V Applicant Reported Findings

Primary Objective	Question # and Text	Normal Literacy (95% CI) N = 379	Low Literacy (95% CI) N = 113	Users (95% CI) N = 25	Non-Users (95% CI) N = 467	Asthma Sufferers (95% CI) N = 87	Non-Asthma Sufferers (95% CI) N = 405	Total (95% CI) N = 492
Prime before first use	*#1: Brenda just purchased* (b) (4) *What does she need to do to get a new inhaler ready for use?*	92% (89%, 95%)	75% (66%, 83%)	76% (55%, 91%)	89% (86%, 92%)	84% (74%, 91%)	89% (86%, 92%)	88% (85%, 91%)
Place finger on center of dose indicator	*#2: Mike needs to take an inhalation to treat his asthma attack. To properly take an inhalation or puff where should he place his finger?*	93% (90%, 95%)	86% (78%, 92%)	80% (59%, 93%)	92% (89%, 94%)	85% (76%, 92%)	93% (90%, 95%)	91% (88%, 94%)
Prime the inhaler again if it is wet	*#3: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do?*	89% (85%, 92%)	75% (66%, 83%)	76% (55%, 91%)	86% (83%, 89%)	79% (69%, 87%)	87% (83%, 90%)	86% (82%, 89%)
Prime the inhaler again if it is not used for 2 days	*#4: Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?*	87% (83%, 90%)	69% (60%, 77%)	80% (59%, 93%)	83% (79%, 86%)	84% (74%, 91%)	83% (79%, 86%)	83% (79%, 86%)

Source: Narrative Response to the Statistical Information Request dated September 6, 2016

5. Label Comprehension Study VI

Design and Conduct

Based on these results, it was determined a further change to the package insert IFU was needed. The formatting was changed for the Prime (Shake and Spray into air) the Inhaler Again subsection to increase user recognition.

Label Comprehension VI was a single-visit study designed to address comprehension of the following primary objectives:

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

The study was conducted in four mall sites: Tampa, FL; Silverdale, WA; Roseville, CA, and Lawrenceville, GA.

Although initial priming failed to do well with low literacy participants in LCS V, the Applicant asserts that this objective was not subsequently tested in LCS VI because "*comprehension had already been successfully demonstrated in LCS II, III, and V*". I question this assertion. In LCS II and III, initial priming was an *informational* objective only – meaning that the Applicant assigned no critical importance to it - and the associated question asked about only *how many times* the inhaler needed to be primed before first time use. It assumed that participants had existing knowledge about *the need* for priming; consequently *the need* to prime was not asked about.

A total of 485 completed interviews took place. Table 5 displays the demographics for the sample. Of note, the sample had good Hispanic representation at 13%, but poorer low literacy representation than the previous two studies, at only 20%. This poor LL representation is ironic as the study protocol had identical exclusion criteria to LCS IV and V, with one exception: an additional criterion stating that : "*If demographic diversity and/or characteristics were not at appropriate levels some exclusion may be used to bring in the needed diversity."* It is clear that this strategy did not lead to an acceptably sized low literacy cohort for reasons that are not clear.

The Applicant acknowledges that the LL representation at 20% "*is somewhat lower than what was described in the study protocol, but is a sufficient subgroup size to make comparisons between normal and low literacy participants*". While this may be true, the goal of 25% low literacy is not only to make comparisons between the populations but also to have a representative general population estimate with which to assess achievement of target thresholds.

Approximately 17% of the sample reported suffering from asthma, with a slightly higher proportion among low literacy than normal literacy participants. The Primatene Mist user cohort included only 31 participants (6%) but demographic characteristics were not significantly different from the non-user cohort.

Table 5: LCS VI Demographics by Literacy

Demographic Characteristics for Subjects by Literacy
(Survey Population)

Responses	All Combined (N=485)	Normal Literacy [1] (N=387)	Low Literacy [2] (N=98)
Gender			
Male	277 (57%)	213 (55%)	64 (65%)
Female	208 (43%)	174 (45%)	34 (35%)
Race			
White	268 (55%)	229 (59%)	39 (40%)
Black or African American	91 (19%)	64 (17%)	27 (28%)
Hispanic	63 (13%)	49 (13%)	14 (14%)
Asian	25 (5%)	18 (5%)	7 (7%)
Native Hawaiian or Other Pacific Islander	5 (1%)	5 (1%)	0 (0%)
American Indian or Alaska Native	4 (1%)	2 (1%)	2 (2%)
Refused	1 (0%)	1 (0%)	0 (0%)
Other	28 (6%)	19 (5%)	9 (9%)
Education Level			
8th grade or less	7 (1%)	2 (1%)	5 (5%)
Some high school	59 (12%)	36 (9%)	23 (23%)
High school graduate, GED, or certificate	142 (29%)	105 (27%)	37 (38%)
Some college or technical school	205 (42%)	176 (45%)	29 (30%)
College graduate	60 (12%)	56 (14%)	4 (4%)
Post-graduate degree	12 (2%)	12 (3%)	0 (0%)
Age Group Category			
16 - 17	26 (5%)	18 (5%)	8 (8%)
18 - 34	306 (63%)	234 (60%)	72 (73%)
35 - 44	54 (11%)	42 (11%)	12 (12%)
45 - 54	44 (9%)	42 (11%)	2 (2%)
55 - 64	31 (6%)	27 (7%)	4 (4%)
>=65	24 (5%)	24 (6%)	0 (0%)

Responses	All Combined (N=485)	Normal Literacy [1] (N=387)	Low Literacy [2] (N=98)
Age Distribution			
Mean (SD)	32 (15)	33 (16)	27 (10)
Median	26	27	23
Range	16 - 86	16 - 86	16 - 59
Asthma Sufferer			
Yes	84 (17%)	64 (17%)	20 (20%)
No	398 (82%)	320 (83%)	78 (80%)
Don't know	3 (1%)	3 (1%)	0 (0%)
Primatene Mist User			
Yes	31 (6%)	26 (7%)	5 (5%)
No	454 (94%)	361 (93%)	93 (95%)

Source: LCS VI Study Report, NDA submission

Applicant-Reported Findings

As Table 6 illustrates, although the normal literacy population scored well on the priming objectives, the low literacy population did not score as well. Comprehension of "prime the inhaler again if it is wet" was 86%, with a LB of 77%, and comprehension of "prime the inhaler again if it is not used for two days" was 80%, with a LB of 70%. Again, former Primatene users directionally had lower comprehension than Primatene non-users.

Table 6: LCS VI Applicant Reported Findings

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

Source: Narrative Response to the Statistical Information Request dated September 6, 2016

6. Other Issues

6.1 Human Factors (Study G3) Videotapes

Since the low literacy findings about priming were less than optimal, I reviewed several of the subsequent human factors videotapes of low literacy asthma inhaler adult users to obtain further qualitative insights as to these findings. In this study, each subject was provided with the revised, streamlined IFU and asked to read it while the interviewer left the room. When the subject had finished reading the IFU, s/he summoned the interviewer to return. The subject was then asked to demonstrate various aspects of using the product. All of the subjects did read the IFU to some extent. However:

- Subject (b) (6) did not prime before initial use or re-use. He did not understand how the dose indicator worked. The G3 Engineering Report also discusses this subject's interview in depth, stating that "*he was an inhaler experienced participant who struggled to read the instructions and was likely not fully functionally literate...he did not recognize a number of words used in the IFU. Throughout the session, he responded to several different questions about the inhaler saying that he simply could not find the information in the instructions...he frequently referred to what he does with his own inhaler.*"

- Subjec (b) (6), a former Primatene user, did not spray when priming either for initial use or repeat use. None of the asthma products he has used involve spraying. He also stated that he would not want to spray a lot as that would use up medicine.

- Subject (b) (6) a former Primatene user, primed by shaking and spraying once. This subject did not understand how the dose indicator worked.

- Subject (b) (6) primed initially by holding the product horizontally, with middle finger near/on dose indicator. This subject eventually demonstrated use with vertical hold, but still appeared not to be pressing on center of dose indicator. This subject also had difficulty pulling the top out to wash the product, and didn't understand the dose indicator.

- Subject (b) (6) appeared to have a product that did not come fully assembled out of the box, although the extent of the problem was unclear.

Regarding Subject (b) (6) issue, this reviewer sent an IR to the Applicant to ascertain if there had been other recorded instances of this problem in the study. The Applicant explained in its response that (b) (4)

The Applicant goes on to state that it reviewed all of the study videos after receiving the IR. Four of 151 videos were not available due to technical issues; two additional videos "did not capture the removal by the participant of the product from the carton". Of the 145 participants for which a video was available, the device was not assembled (ie, canister was not secured in the actuator) for five, or 3.4% (5/145) study participants. The Applicant asserts that all were able to effectively reposition the canister into the actuator, and concludes that in any case this separation was an artifact of Study G3 and will not occur in the commercial product.

I recommend that the manufacturing experts be contacted for review and comment.

6.2 Underlying assumptions of the Applicant regarding user population

The Applicant states in the NDA resubmission that the benefit/risk equation is favorable in light of the human factors and bench testing results. However, the G3 Engineering Report does not characterize Primatene's anticipated user group as identical with the labeled indication. Its definitive conclusion on page 15 states: *Based on activities outlined in this report, including the final Human Factors Validation Study,* (b) (4) "temporary relief of mild symptoms of intermittent asthma".

Additionally, this report's characterizations of the anticipated user group contain two other inconsistencies:

- Page 15 also states: "*failure to properly complete this sequence (of initial priming) may result in the user receiving a slightly higher or lower dose of medication for the first several sprays, which in turn could result in incomplete relief of their mild to moderate asthma symptoms.*"

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

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

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

The Applicant states that it would be difficult to field such a study because mild sufferers only have occasional episodes; consequently it asserts that most episodes involving Primatene use would probably be beyond the timeline scope of a study. While this is a valid point, I believe that the Applicant could advertise for sufferers of mild symptoms of intermittent asthma (in other words, the labeled indication for this product) and then assess whether the sufferers' definition of "mild" and "intermittent" is in fact aligned with the Applicant's definition of "mild", and "intermittent" by assessing actual patterns of usage and any difficulties with the use of the product.

6.3 Web-Based Labeling

In an April 14, 2014 correspondence with FDA, the Applicant wrote that "*although a telephone number is currently provided under Drug Facts, a dedicated website is currently under development in order to provide consumers with an additional resource should questions arise. The website will allow 24 hours a day/7 days a week access for consumers with questions regarding the proper use of the product.*"

The Applicant clarified in a July 22, 2016 IR response that there was a website link on the DFL. The Applicant also stated that the website content was currently in progress, and that the website would include final label content highlighting precautionary information, an instructional video, highlights of the changes between Primatene Mist and (b) (4) (and impact on product use) and additional resources for asthma. The Applicant committed to providing a draft of the website content in mid-August, which was in the midst of the NDA review cycle.

The subsequent website draft submitted by the Applicant on August 17, 2016 (shown in Appendix 5) contains:

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

The summary page entitled (b) (4) highlights the changes between the old and new formulations. However, it states that the (b) (4) indicator, "*shows how many sprays of medication you have left in the container*." It does *not* highlight the important caveat that the dose indicator does not move with every spray. Therefore, I believe this could be considered to be a somewhat misleading statement on labeling in that it does not provide a fuller description of how the dose indicator works, and should be revised accordingly.

The Asthma Learning Center is highly informative and educational with regard to asthma triggers; this discussion would probably be helpful to many sufferers and in that sense it is a great example of how website labeling can expand upon useful information for which there is no real estate on the Drug Facts Label. My concern about the Center is that while it states up front that asthma is a serious disease that should be diagnosed by a doctor, there is little discussion of the potential necessity of some kind of physician monitoring on an ongoing basis (other than reference to an Asthma Plan, which is not defined) and no discussion or definition of what the labeled indication of "mild symptoms of intermittent asthma" actually means. At the very least, the (b) (4)" section should be positioned up front and center, instead of at the end. As page 15 of the G3 Engineering Report states, there is no expectation on the part of the Applicant that users of the product will be under the care of a healthcare professional for their intermittent asthma. If that is the case, while the availability of this product may provide a workable solution

for those consumers who otherwise would have limited or no access to asthma medication, there may additional opportunities in the Asthma Learning Center with which to educate them more adequately about their disease.

7. Conclusions and Recommendations

From a consumer research perspective, since the labeling was significantly revised after LCS VI, the key research input for an approval decision is the human factors study. Additionally:

- The Applicant should be asked to justify [redacted] and determined by the Applicant afterward to be of low risk.

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

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

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

- CMC reviewers should confirm that the packaging issues identified by this reviewer with regard to the human factors study would not be anticipated to continue in a product launch scenario.

Appendices

APPEARS THIS WAY ON ORIGINAL

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

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA R COHEN
11/21/2016

FRANCIS E BECKER
11/25/2016

Medical Officer Memorandum
Division of Pulmonary, Allergy, and Rheumatology Products

Date:	May 21, 2014
From:	Susan Limb, MD Clinical Team Leader, DPARP
Through:	Sally Seymour, MD Deputy Director of Safety, DPARP
Through:	Badrul Chowdhury, MD, PhD Director, DPARP
NDA/IND:	Epinephrine HFA inhalation aerosol, NDA 205920
Subject:	Device and dose indicator performance assessment

Materials reviewed: Device performance evaluation supplement reports dated February 24, 2014, and March 18, 2014; response to information request dated April 2, 2014, and May 12, 2014

Executive Summary

The reliability and performance of the device and dose indicator are critical factors in the risk-benefit assessment for epinephrine HFA inhalation aerosol, which is proposed for use as an over-the-counter (OTC) treatment (b) (4) There are multiple steps required for shaking, priming, actuation, and cleaning in order to ensure adequate product performance, and data from patient diaries and assessment of device and dose indicator performance in the clinical trials indicate that OTC consumers may have difficulty using the proposed product correctly. While root-cause analysis conducted by the Applicant has not identified a specific defect inherent to the product, the overall reported rate of device malfunction from the clinical trials (7%) and the nature of many of the reported malfunctions (clogging and improper spray; 43% of device malfunction reports) raise concern regarding the usability of the product and consumer perception of reliability and performance. In terms of the dose indicator, the number of reported errors, particularly undercounting errors, also raises concerns about its ease of use. Therefore, the Division recommends that the Applicant further characterize potential sources of user error and refine labeling and the device, if indicated, to minimize user error and improve the usability of the product.

Background

Armstrong Pharmaceuticals submitted NDA 205-920 on July 22, 2013, for epinephrine HFA inhalation aerosol, proposed for OTC marketing for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. The proposed product is a (b) (4) suspension containing epinephrine as the active ingredient, HFA-134α as the propellant, dehydrated alcohol (b) (4) polysorbate 80 (b) (4) and thymol (b) (4) delivered via a metered-dose inhaler (MDI). The MDI components include a 14 ml aluminum canister with a (b) (4) valve (Model (b) (4), 50 µl metering (b) (4))

and [redacted] L shape orange actuator with a [redacted] orifice). The MDI is fitted with a [redacted]-count top-mount dose indicator [redacted]

The Agency views an inhalation aerosol product such as the proposed epinephrine HFA to be the sum of its parts, i.e., the product entails all of the device components, the formulation, and any necessary protective packaging. In general, dose delivery is influenced not only by the device components but also by the formulation and any interactions between the formulation and the device components. Even if various device components and formulations have been found to be acceptable in other products, the same performance characteristics cannot be guaranteed for new combinations in new products. Therefore, the Agency requires an evaluation of product performance for all new MDI asthma products. Such an evaluation typically includes in vitro assessment of ruggedness and reliability, root-cause evaluation of all device complaints, and testing of a random sampling of clinical trial device units. Likewise, while dose indicators are generally considered a favorable addition to an MDI product, the Agency expects a demonstration of reliability and accuracy in the clinical program. At multiple interactions with the Applicant during the development program for epinephrine HFA, the Agency advised the Applicant to include information supporting the performance of the drug-device product in the NDA.

The original submission for epinephrine HFA presented summary information on device and dose indicator performance, including a summary of the root-cause analysis performed for the reported malfunctions. The Applicant concluded that the majority of reported problems were attributable to user error and inconsistent subject diary information, and the evaluation did not identify a problem inherent to the product. Despite the Applicant's conclusions, the Agency had concerns given the number and nature of the device malfunctions and dose indicator errors reported in the clinical program. Potential user error is a concern for a product proposed for OTC use. Also, the original submission did not include sufficient detail for the Agency to confirm the Applicant's conclusions from the root-cause analysis. These issues were reflected in the Agency's briefing document and presentation materials for the February 25, 2014, Nonprescription Drugs Advisory Committee (NDAC) meeting. A copy of the Agency's NDAC presentation on CMC/device issues with annotated references is provided in an appendix to this document.

In response to the Agency's concerns, the Applicant submitted additional analyses of device and dose indicator performance on February 24, 2014, and updated analyses on March 18, 2014. The Applicant also submitted responses to information requests on April 2, 2014, and May 12, 2014. The February 2014 supplemental report stated that the additional analyses were based on data generated prior to NDA filing, and the March 2014 supplement report was intended to provide additional information on the analyses presented in the earlier amendment. Given the timing of these submissions, the Agency did not have time to review the information prior to the February 25, 2014, NDAC meeting, and the Agency's briefing document and presentation at the meeting were based on the original July 22, 2013, submission. This memorandum focuses on the information included in the subsequent amendments from a clinical perspective. Separate reviews of product performance from a CMC perspective can be found in the CMC reviews dated April 23, 2014, and April 29, 2014. A review of label comprehension and behavior

studies, which assessed consumer understanding of instructions for use, can be found in the social science review dated May 5, 2014.

As the Applicant categorized device malfunction and dose indicator errors separately, this memorandum also addresses these issues separately.

Device Malfunction Evaluation

Malfunction reports

The original submission stated that 251 out of 3508 (7%) returned MDI units from the clinical trials (Trials C, C2, and D) that were eligible for evaluation were reported as having a device malfunction. Of these, 53 were reported as having clogging issues and 31 were reported as not dispensing properly. Clogging and improper spray are problems of particular interest given the Agency's past experience with other HFA MDI products. Details on the remaining 167 units were not provided in the original submission. Additional information on the number and nature of the malfunction reports was provided in the February and March 2014 amendments. The Applicant states that 4,249 units were returned for malfunction assessment, of which 3,752 were eligible for evaluation. A total of 495 returned units were unused and were therefore excluded from evaluation, while another 2 returned units had incomplete information and were also excluded. Based on the new submissions, the overall malfunction report rate remains 7% (251 of 3,752). Of the 3,752 returned eligible units, 61 (2%) were reported as clogging or suspected clogging and another 47 (1%) were reported as not dispensing properly or having an improper spray.

Two of the reported malfunctions which were not categorized as potential clogging/improper spray issues are worth noting. One unit (PMFU ID (b) (4)) was reported as a leakage problem, but notes from the patient interview state that the patient reported needing extra priming sprays and the absence of a spray despite cleaning and reassembling the inhaler. Another unit (PMFU ID (b) (4)), which was categorized as having an "appearance" issue due to a white film on the canister, was also noted to not be dispensing properly and required extra priming sprays. Details of the other reported malfunctions are shown in Table 1.

Table 1 Reported device malfunctions in Trials C, C2, and D	
Reported malfunction	**Number of MDI units**
No detail	69
Clogging	53
Suspected clogging	8
Not dispensing properly	31
Improper spray	16
Dose indicator moves incorrectly	38
Dose indicator issue	7
Dose indicator jump	3
Dose indicator overcount	1
Dose indicator stuck	1
Improper assembling	1
Patient use error	3
eDiary error	4
Dirty	7
Brown residue	1
Broken	2
Canister cannot be pushed down	1
Malfunction	2
Leak	3
Total	**251**

Source: Applicant's February 24, 2014 submission, Table 5

Malfunction assessment

The original July 2013 submission stated that all 251 units reported as malfunction performed within release specifications upon testing and concluded that the malfunction reports were likely secondary to errors in use or in recording. As the details of the testing and results of the root cause analysis were not provided in the original submission, the Agency was unable to confirm these conclusions. The Applicant provided more detail on the malfunction evaluation in the February and March 2014 amendments. To evaluate the devices for clogging issues, testing included dosage evaluation (shot weight) and proper dispensing. Shot weight was measured after priming the unit once then measuring the weight difference after one spray. Proper dispensing was assessed by observation for "Normal = spray out as a gas stream," "No Spray," or "Scattered."

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

Of the 251 reported malfunctioning units, a total of 245 units underwent testing for shot weight and proper dispensing and were deemed to be functioning properly on root cause analysis. The malfunction reports for these 245 units were subsequently attributed to errors in use or reporting. While the Applicant's assessment did not identify a specific device issue, the review notes that 9 reports of clogging or improper spray appeared to resolve with extra cleaning performed by the

patients.[1] One patient reported cleaning the device 2-3 times per day due to clogging, and visual inspection of the device in the clinic revealed accumulation of medication inside the mouthpiece (PMFU ID (b) (4)). There were 22 reports of clogging or improper spray that appeared to resolve with extra sprays performed by the patients,[2] and 4 reports of clogging that resolved with a combination of extra cleaning and additional sprays.[3] It is not possible to determine whether these additional actions performed by the patients may have mitigated a clogging/improper spray problem prior to testing.

The 6 units which were not tested included 4 empty units (PMFU ID (b) (4)), the unit with the broken valve stem (PMFU ID (b) (4)), and PMFU ID (b) (4). PMFU ID (b) (4) was reported for a stuck dose indicator but was not tested for shot weight or proper dispensing, and a reason is not provided. Another unit (PMFU ID (b) (4)) was returned empty but was reported to have passed testing for shot weight and proper dispensing.

Dose Indicator Performance

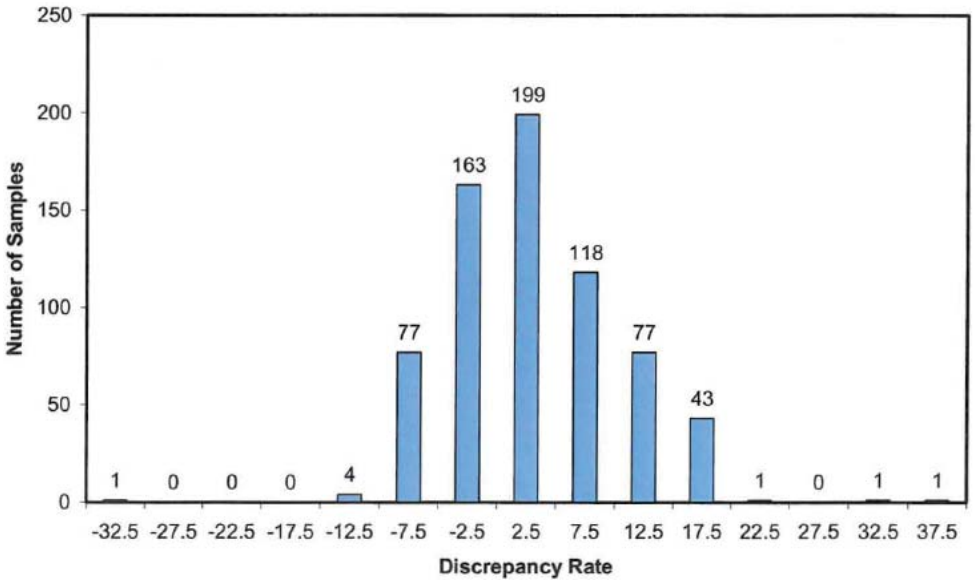
Performance assessment based on e-diary records

The original submission dated July 22, 2013, included an evaluation of dose indicator performance based on e-diary records. The Agency had concerns about the submitted analysis, including the large number of returned units which appeared to be excluded from the analysis and the justification for the proposed acceptance criteria. For example, out of 2772 units returned in Trial C, 1370 units ultimately qualified for performance assessment. The other 1402 units were disqualified for a variety of reasons, the rationale for some of the exclusions being unclear. For example, if 2 units were dispensed at one study visit but only 1 unit had any records to support usage, both units were omitted from the analysis. In terms of acceptance criteria, the Applicant proposed a threshold of <10% for undercounting and >20% for overcounting, stating the dose indicator errors falling in this range were unlikely to represent a safety risk. The distribution of dose indicator/e-diary error from Trials C and C2 are shown in Figure 1 and Figure 2, respectively. In Figure 1, one sample represented two MDI units, whereas in Trial C2, one sample represented one MDI unit. A distribution for Trial D was not provided.

[1] PMFU ID: (b) (4)
[2] PMFU ID (b) (4)

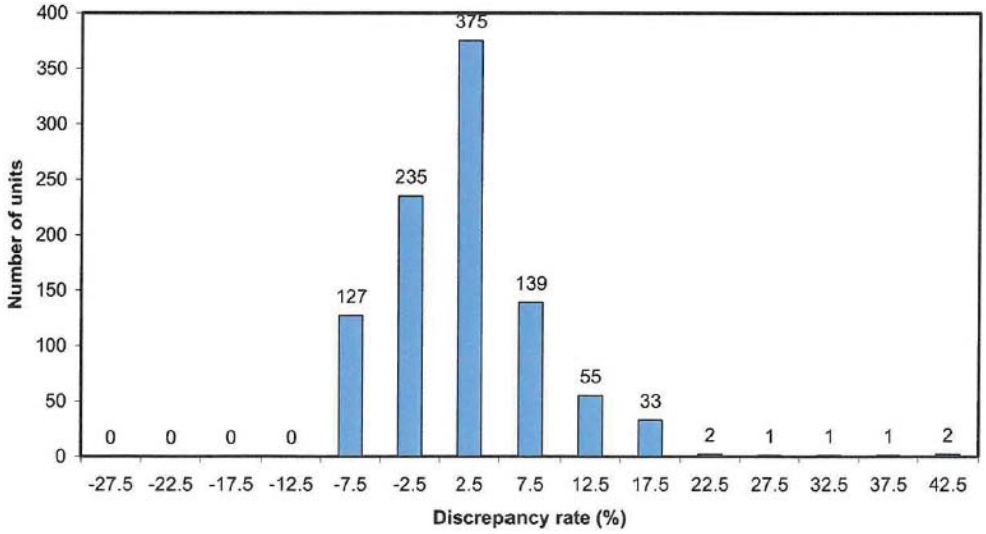
PMFU ID: (b) (4)

Figure 1 Distribution of dose indicator/e-diary discrepancy rate for Trial C (1 sample = 2 units)



Source: Applicant's July 22, 2013 submission, Final report for performance evaluations of E004 clinical units for Studies API-E004-CL-C, C2, and D, Figure 1

Figure 2 Distribution of dose indicator/e-diary discrepancy rate for Trial C2 (1 sample = 1 unit)



Source: Applicant's July 22, 2013 submission, Final report for performance evaluations of E004 clinical units for Studies API-E004-CL-C, C2, and D, Figure 2

Based on this analysis, the Applicant concluded for Trial C that 5 out of 685 samples (0.7%) had an undercount that exceeded the proposed 10% threshold and 3 samples (0.4%) had an overcount that exceeded the 20% threshold. For Trial C2, no samples had an undercount that exceeded the 10% threshold and 7 out of 971 qualified samples (0.7%) had an overcount exceeding the 10% threshold. On follow-up testing, the Applicant states that the force required to actuate the MDI

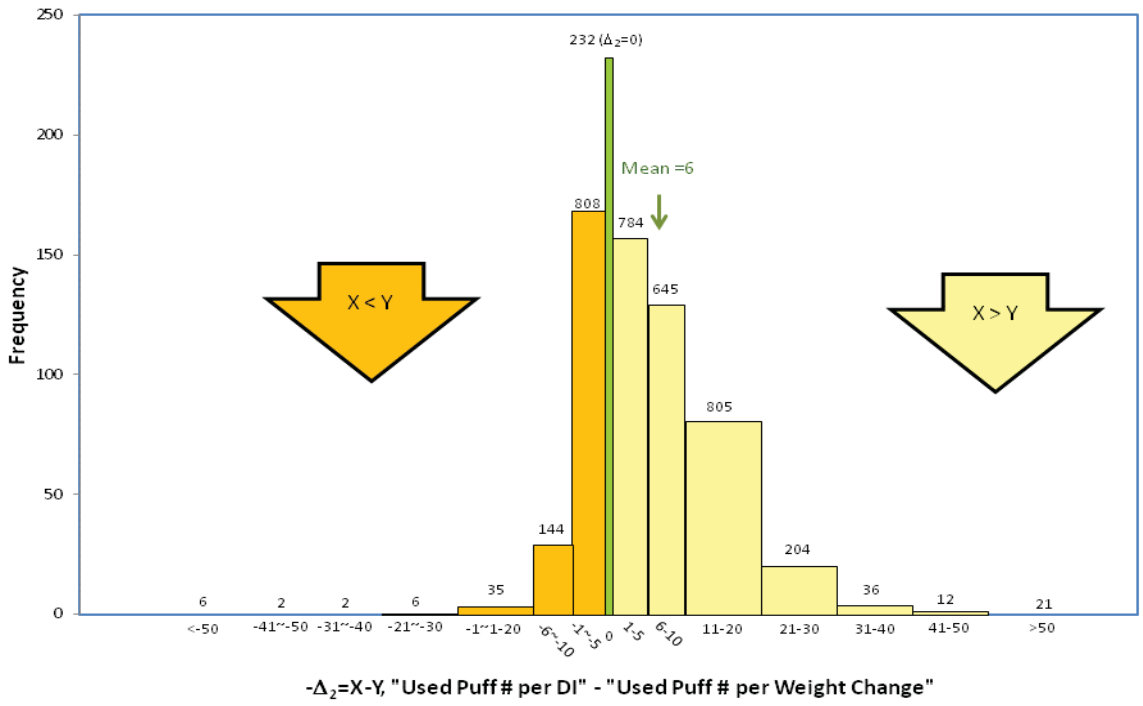
exceeded the force required to trigger the dose indicator for the 5 samples exceeding the 10% undercount threshold. Based on this analysis, the Applicant concluded that the reported undercounting was likely secondary to incorrect use, such as pressing on the side of the dose indicator or double spraying the unit without complete release of the unit valve between sprays. Similarly, the Applicant concluded that the reported cases of overcounting were likely due to dropping the unit or incorrect use.

Performance assessment based on unit weight change

The February and March 2014 amendments provided more information on the disposition of returned units and included an analysis of dose indicator accuracy based on unit weight change. For each returned unit, the number of sprays used and the number of remaining sprays based on weight were each compared to the dose indicator reading. A total of 3,742 units out of 4,249 returned units were assessed for dose indicator performance from Trials C, C2, and D. Per the more recent submissions, a total of 495 units were excluded because they were unused, while the remaining 12 units were excluded because they were broken or no unit weight records were available. (b) (4) Based on the criterion of ≤8 puffs remaining, a total of 13 units (0.4%) were identified as undercounting. Nine of the 13 units were placebo units. The Applicant suggests that this imbalance may be due to patients using excessive pressure or too rapid succession of actuations in an attempt to relieve asthma symptoms.

In an April 2, 2014, response to information request, the Applicant provided the distribution of discrepancies between the dose indicator and unit weight change for the 3,742 units assessed (Figure 3). Based on this analysis, 51 units (1%) undercounted by 11 doses or more and 16 units (0.4%) undercounted by 20 puffs or more. Conversely, 1078 units (29%) overcounted by 11 doses or more and 273 units (7%) overcounted by 20 puffs or more.

Figure 3 Distribution of discrepancy between dose indicator and unit weight change



Source: April 2, 2014, Response to Information Request, Figure 4, NDA 205920

Conclusions

The February 24, 2014, March 18, 2014, April 2, 2014, and May 12, 2014, submissions provide additional information on device malfunctions and dose indicator performance in the epinephrine HFA clinical trials. In general, the submissions address the Agency's previous concerns regarding the exclusion of units from evaluation, providing more information on the disposition of collected units and the reasons for exclusion. This information had not been included in this detail in the original July 22, 2013, submission.

However, concern remains regarding the potential for user error and over user-friendliness of the product given the number and nature of the malfunctions and dose indicator errors reported in the clinical trials. Multiple steps are required for shaking, priming, actuation, and cleaning in order to ensure adequate product performance, and data from patient diaries and assessment of device and dose indicator performance in the clinical trials indicate that OTC consumers may have difficulty using the proposed product correctly. In terms of device malfunctions, the Applicant's root-cause analysis did not identify a specific defect inherent to the product. Yet the reports of apparent user error are noteworthy given the fairly modest size of the clinical trial database, the rigorous daily cleaning instructions, and the known potential concern for clogging associated with other HFA-based aerosol products. In some sense, the clinical trial setting reflects a best-case scenario, as trial participants used the products on a regular schedule and received specific instructions on the use of the product and daily reminders for device cleaning.

How the epinephrine HFA product will perform in the proposed OTC setting without these provisions in place remains an open question.

Likewise, the number of dose indicator errors is a concern, particularly the cases of undercounting, which may lead to false assurance. The threshold for concern is not absolute and varies based on the intended use of the product; for an OTC product intended for the acute relief of bronchospasm, minimizing errors and optimizing ease of use are especially desirable. While the proposed dose indicator for epinephrine HFA appears to function adequately when used with correct technique, the issue of technique underscores the need for a consumer-friendly product. In other words, if the dose indicator requires a certain amount of precision for correct use, e.g., pressing squarely on the center as opposed to the edge or not pressing in too rapid succession, there is some question whether the amount of precision required is reasonable for the OTC setting, where patients will not receive live instruction on the use of the device and access to other healthcare resources may be an issue.

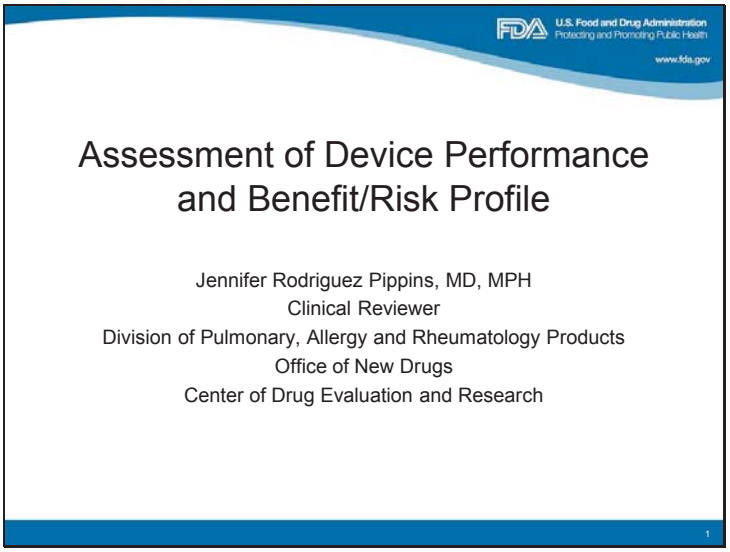
The concerns raised in the clinical trial data coincide with concerns identified in the label comprehension and behavior studies (see Social Science review dated May 5, 2014), regarding consumers' ability to use epinephrine HFA inhalation aerosol for the acute treatment of asthma in an OTC setting. Data from these studies suggest that consumers may not clearly understand how to use the product and might have difficulty executing the fairly complex series of steps required to administer, clean, and maintain the product.

Based on these concerns, the Division recommends that the Applicant further evaluate the product-patient interface to identify sources of potential user error and improve the usability of the product. This evaluation should include reassessment of label comprehension and behavior/human factors via an iterative process followed by a randomized, actual use study with revised labeling and the proposed epinephrine HFA inhalation aerosol to quantify and evaluate complaints or problems associated with use and characterize sources of user error. Assessment of patient complaints or problems with the dose indicator should be included in this study. The Division also recommends that the Applicant include a marketed bronchodilator product as a benchmark comparison in the study.

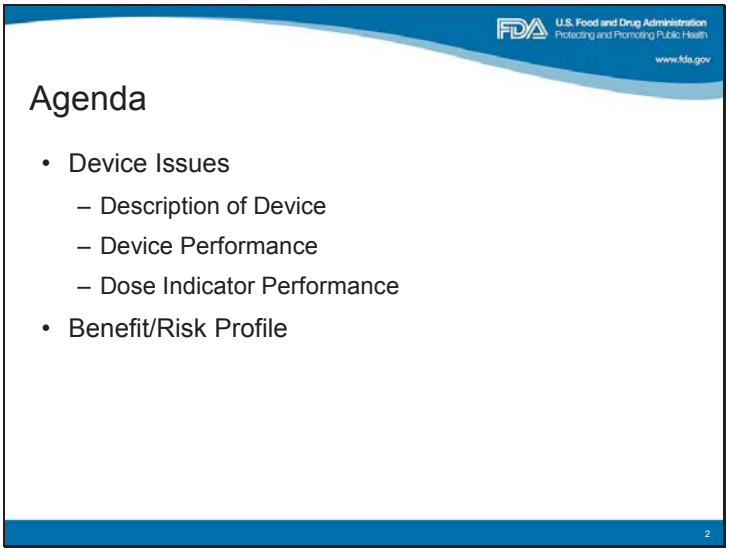
Depending on the results of the above iterative evaluations, modification of the product and/or product labeling may be necessary to minimize potential user error, e.g., revised patient instructions for use, replacement of the current dose indicator with an integrated dose counter, product reformulation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

Appendix: Annotated FDA NDAC presentation (February 25, 2014)

Slide 1



Slide 2


U.S. Food and Drug Administration
Protecting and Promoting Public Health
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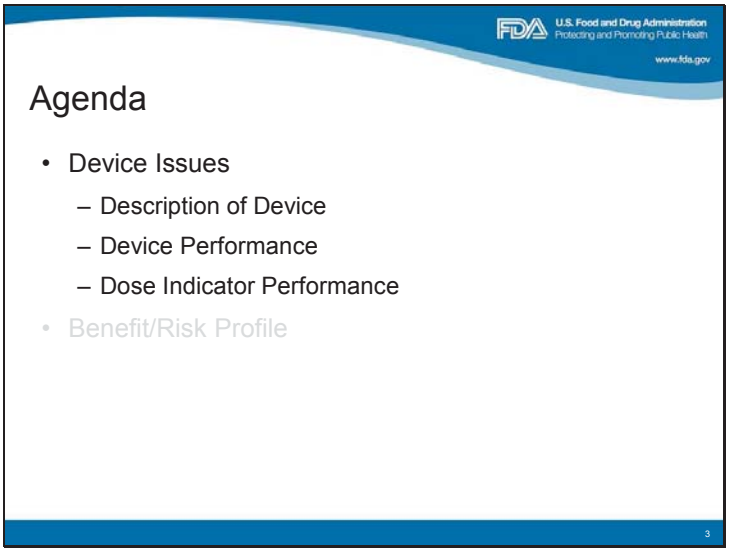
Agenda
• Device Issues
– Description of Device
– Device Performance
– Dose Indicator Performance
• Benefit/Risk Profile
2

Slide 3


U.S. Food and Drug Administration
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Agenda
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Slide 4

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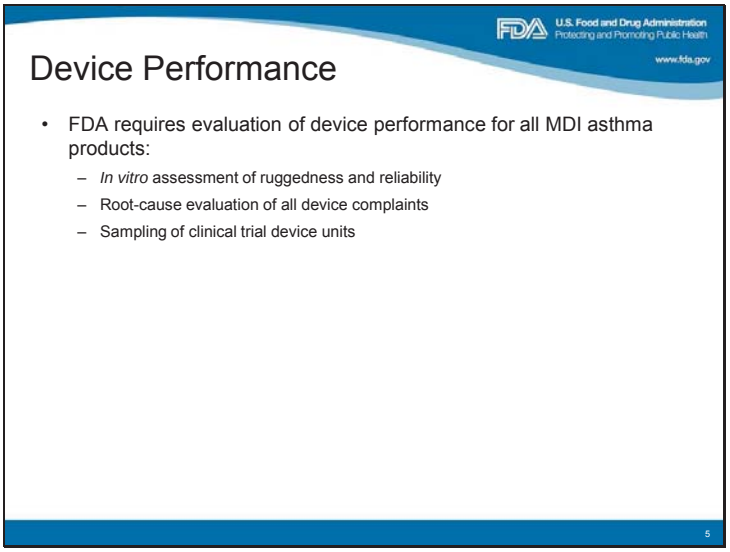
Device

- 14 mL anodized aluminum canister with 50 µL metering valve
- 160-count dose indicator
  - Counts down in 20 dose decrements: 160, 140…20, 0
  - Visual warning (20-0 doses displayed in red zone) to buy new unit

Source: App icant's NDA 205-920 Briefing Document, pg. 87

Slide 5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Device Performance
• FDA requires evaluation of device performance for all MDI asthma products:
– *In vitro* assessment of ruggedness and reliability
– Root-cause evaluation of all device complaints
– Sampling of clinical trial device units
5

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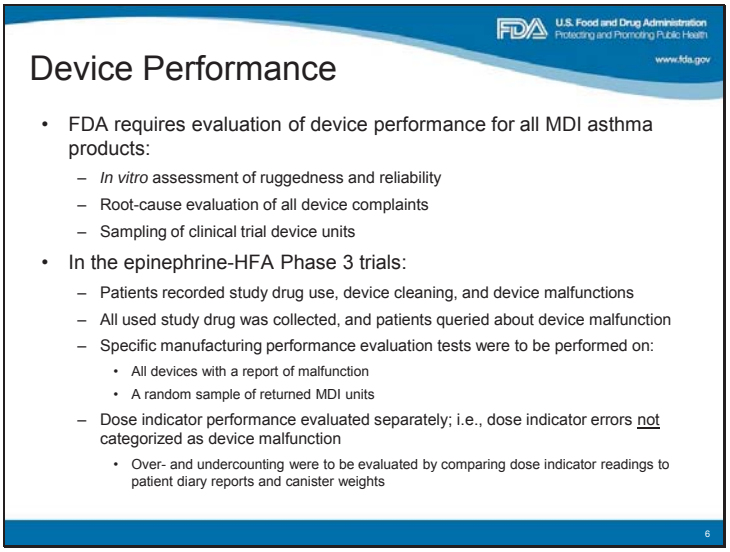
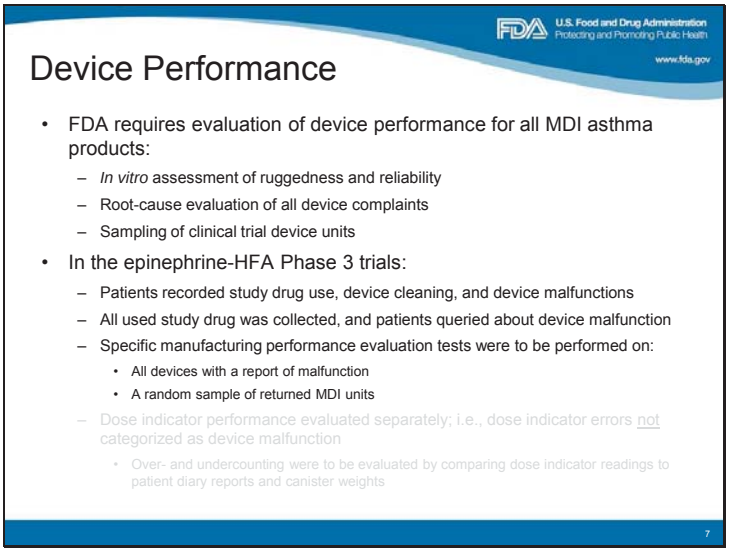
Slide 6


U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov
Device Performance
• FDA requires evaluation of device performance for all MDI asthma products:
– *In vitro* assessment of ruggedness and reliability
– Root-cause evaluation of all device complaints
– Sampling of clinical trial device units
• In the epinephrine-HFA Phase 3 trials:
– Patients recorded study drug use, device cleaning, and device malfunctions
– All used study drug was collected, and patients queried about device malfunction
– Specific manufacturing performance evaluation tests were to be performed on:
• All devices with a report of malfunction
• A random sample of returned MDI units
– Dose indicator performance evaluated separately; i.e., dose indicator errors not categorized as device malfunction
• Over- and undercounting were to be evaluated by comparing dose indicator readings to patient diary reports and canister weights
6

Slide 7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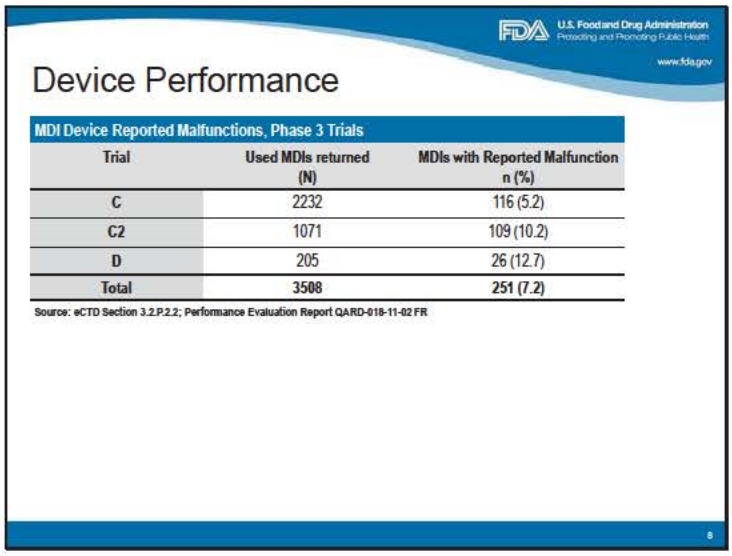
7

Slide 8



Source:

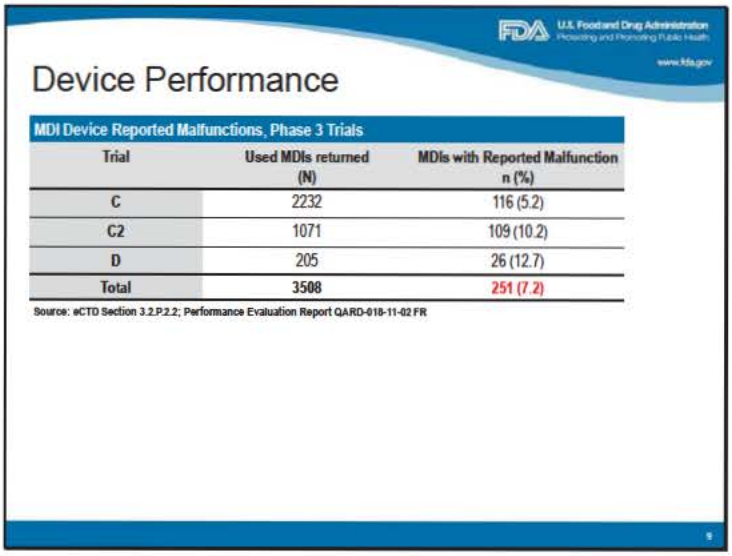
Used MDIs returned:

- **C: n=2232** (NDA 205-920, eCTD Section 3.2.P.2.2; Performance Evaluation Report QARD-018-11-02 FR, Section 3.1.1, pg. 5)
- **C2: n=1071** (Section 3.1.2, pg. 6)
- **D: n=205** (Section 3.1.3, pg. 8)
- **Total: n=3508** (Reviewer's calculation: 2232+1071+205=3508)

MDIs with Reported Malfunction

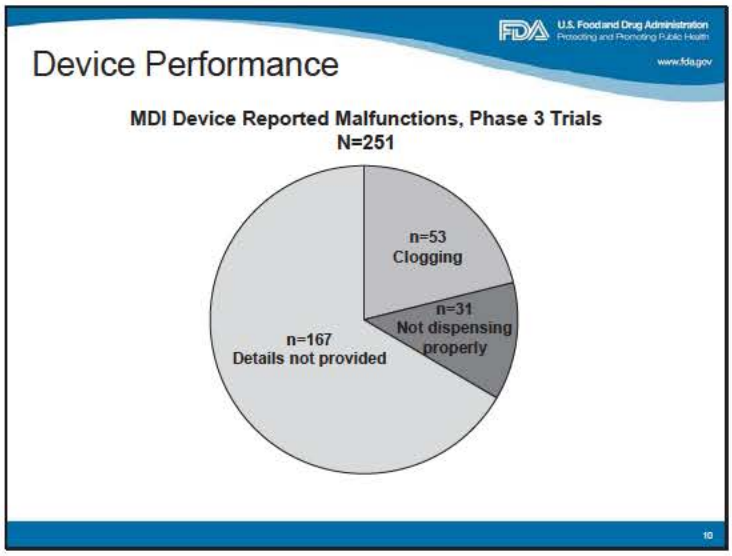
- **C: n=116** (Section 3.1.1, pg. 5)
  5.2% (Reviewer's calculation: 116/2232=5.2%)
- **C2: n=109** (Section 3.1.2, pg. 6)
  5.2% (Reviewer's calculation: 109/1071=10.2%)
- **D: n=26** (Section 3.1.3, pg. 8)
  12.7% (Reviewer's calculation: 26/205=10.2%)
- **Total: n=251** (Section 4.2, Table 16, pg. 18)
  7.2% (Reviewer's calculation: 251/3508=7.2%)

Slide 9



Source: See annotation for Slide 8

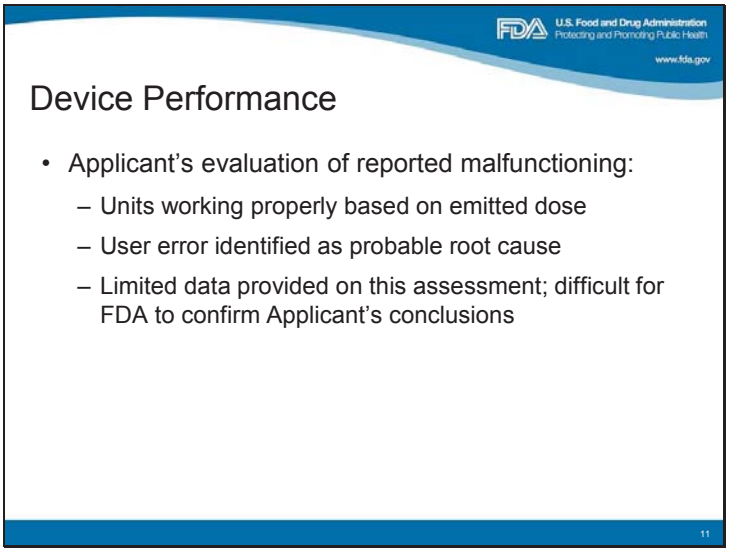
Slide 10



Source:

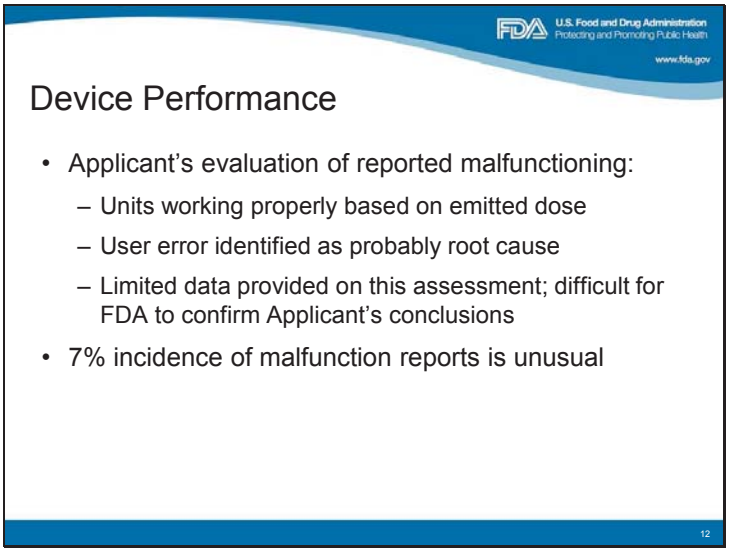
- **N=251** (NDA 205-920, eCTD Section 3.2.P.2.2; Performance Evaluation Report QARD-018-11-02 FR, Section 4.2, Table 16, pg. 18)
- **Clogging: n=53** (Section 4.2, Table 16, pg. 18)
- **Not dispensing properly: n=31** (Section 4.2, Table 16, pg. 18)
- **Details not provided: n=167** (Reviewer`s calculation based on information in Table 16 on page 18: 251-53-31=167)

Slide 11



Source: NDA 205-920, eCTD Section 3.2.P.2.2; Performance Evaluation Report QARD-018-11-02 FR, Section 4.4.4, pg. 33

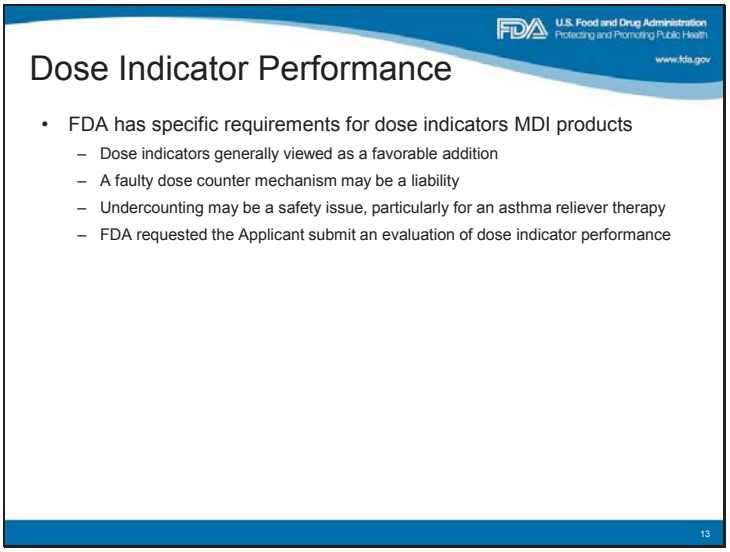
Slide 12



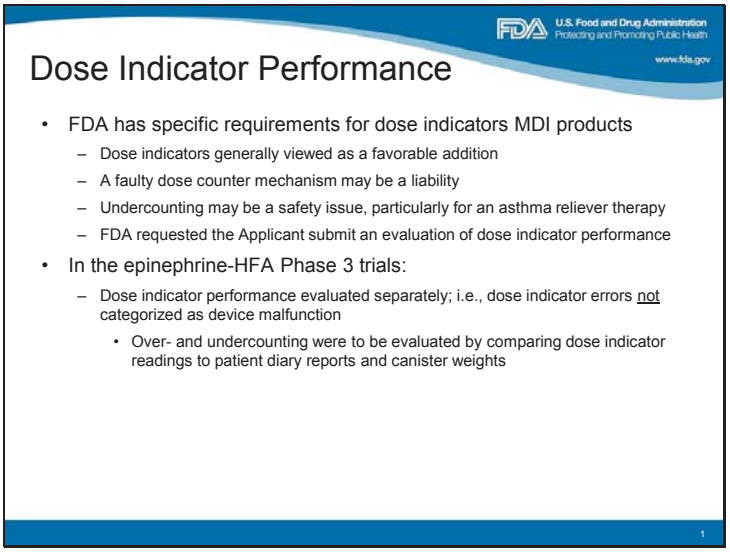
Source:

Incidence of malfunction: 7% (Reviewer's calculation, see annotation for Slide 8)

Slide 13


U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov
Dose Indicator Performance
• FDA has specific requirements for dose indicators MDI products
– Dose indicators generally viewed as a favorable addition
– A faulty dose counter mechanism may be a liability
– Undercounting may be a safety issue, particularly for an asthma reliever therapy
– FDA requested the Applicant submit an evaluation of dose indicator performance
13

Slide 14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– FDA requested the Applicant submit an evaluation of dose indicator performance
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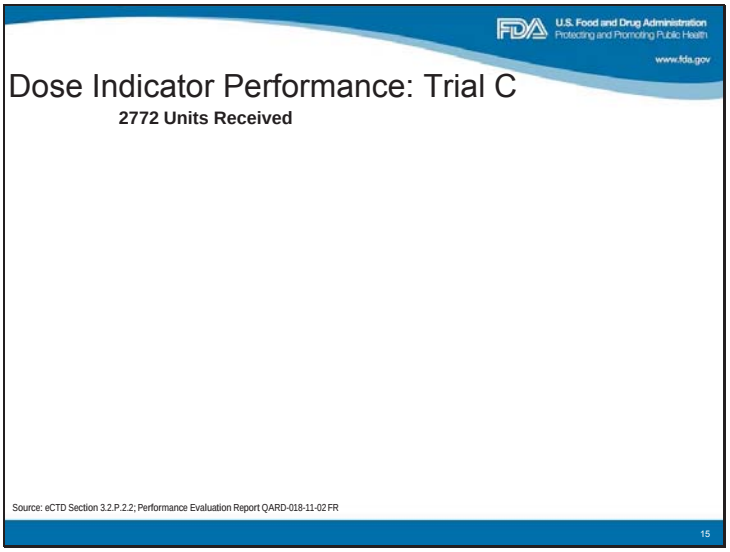
– Dose indicator performance evaluated separately; i.e., dose indicator errors not categorized as device malfunction
• Over- and undercounting were to be evaluated by comparing dose indicator readings to patient diary reports and canister weights
1

Slide 15



Source:

Units Received: n=2772 (NDA 205-920, eCTD Section 3.2.P.2.2; Performance Evaluation Report QARD-018-11-02 FR , Section 3.1.1, Table 1, pg. 6)

- **Units Excluded: n=504** (Reviewer's calculation 2772-2268=504)
  - **Improper e-diary: n=309** (Section 4.3.1, pg. 19)
  - **Either unit unused: n=176** (Section 4.3.1. pg. 19)
  - **Other: n=19** (Reviewer's calculation 504-309-176=19)
- **Units Included: n=2268** (Section 4.3.1, pg. 19); **Samples: n=1134** (Section 4.3.1, pg. 19)
  - **Samples Omitted[1]: n=360** (Reviewer's calculation based on information provided on page 20, Section 4.3.1.1, Table 17: 164+196=360)
    - **E-diary > than max. puffs: n=164** (Section 4.3.1.1, Table 17, pg. 20)
    - **E-diary < than min. puffs: n=196** (Section 4.3.1.1, Table 17, pg. 20)
  - **Samples Retained: n=774** (Section 4.3.1.1, Table 17, pg. 20)
    - **Samples Disqualified[2]: n=89** (Section 4.3.1.2, Table 22, pg. 24)
      - **Undercounting: n=25** (Section 4.3.1.2, Table 18, pg. 21)
      - **Overcounting: n=64** (Section 4.3.1.2, Table 20, pg. 23)
    - **Samples Qualified[3]: n=685** (Section 4.3.1.2, Table 22, pg. 24)
      - **Samples: n=1370 units** (Reviewer's calculation based on data regarding conversion between units and samples found on page 19, Section 4.3.1)
      - **Percentage: 49%** (Reviewer's calculation: 1370/2772=49%)

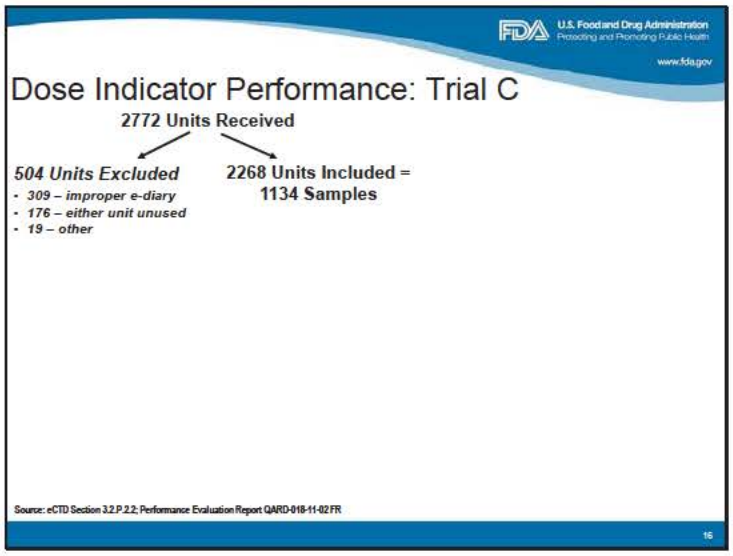
[1] The FDA slide uses the terminology "samples omitted'; while this differs from the language in the Applicant's Table 17 (which discusses samples that were "qualified" or not), FDA's use of the term "omitted" is consistent with the language found in the sentence preceding the table which states "Clinical units for which the e-dairy records were either higher than the maximum dosages or lower than the minimum dosages were excluded for dose indicator evaluation" (page 20, Section 4.3.1.1). FDA

chose to use the term “omitted” in place of the Applicant’s term “excluded” to distinguish the data from the exclusions discussed on pages 18-19, Section 4.3.1 of the Applicant’s report, and in place of the Applicant’s terminology regarding “qualified samples” (or, by extension, not qualified samples) to distinguish these data from the “disqualified samples” discussed on page 24, Section 4.3.1.2, Table 22 of the Applicant’s report.

[2] The FDA slides uses the terminology “retained,” which differs from the language in the Applicant’s Table 17 (which discusses samples that were “qualified” or not). FDA chose to use the term “retained” in place of the Applicant’s term “qualified” to distinguish it from the “qualified samples” discussed on page 24, Section 4.3.1.2, Table 22 of the Applicant’s report.

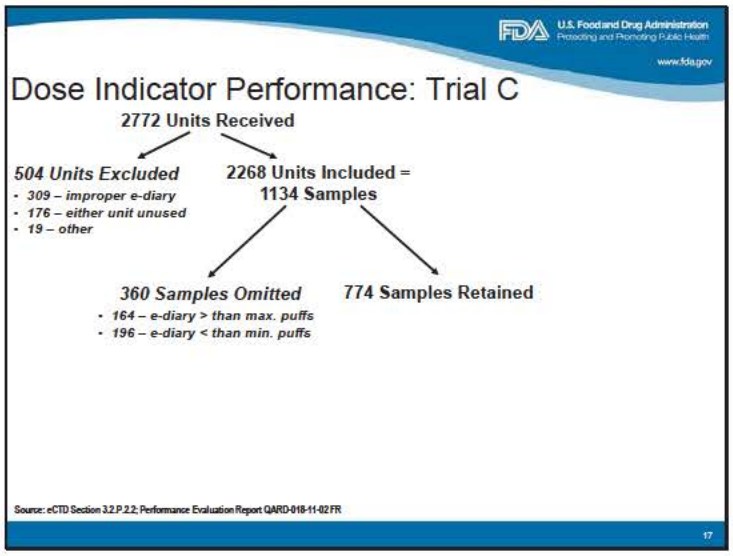
[3] The FDA slide uses the terminology “samples disqualified,” which differs from the language used on pages 20 and 22, Section 4.3.1.2 of the Applicant’s report (which discusses samples that were “excluded”). FDA’s chose to use the term “disqualified” to distinguish these data from the exclusions discussed on pages 18-19, Section 4.3.1 of the Applicant’s report.

Slide 16



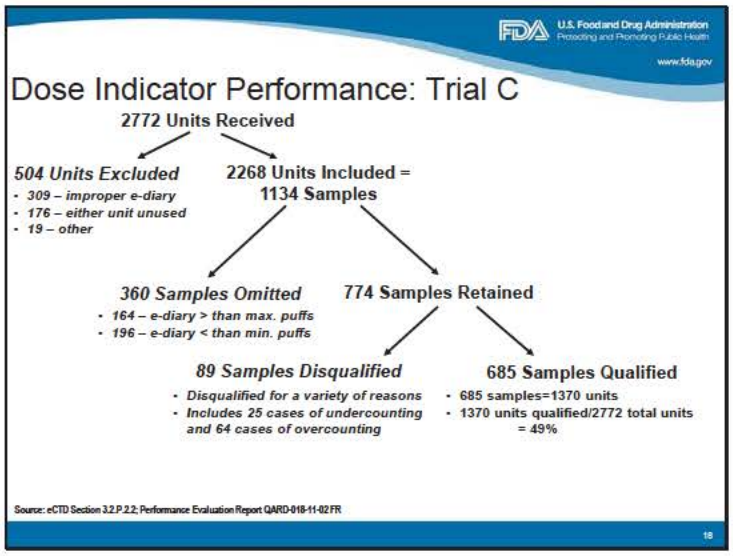
Source: See annotation for Slide 15

Slide 17



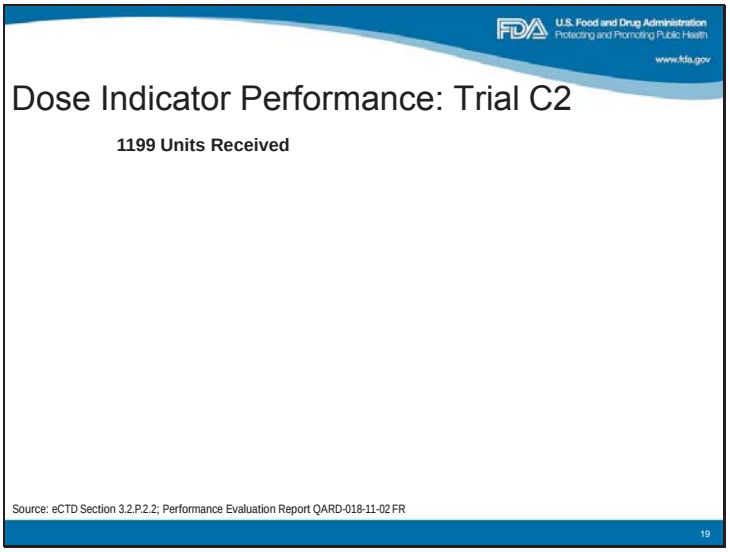
Source: See annotation for Slide 15

Slide 18



Source: See annotation for Slide 15

Slide 19

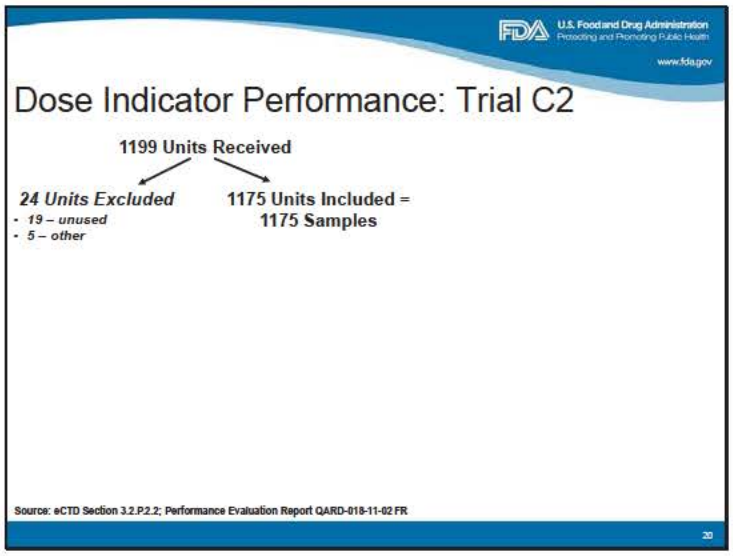


Source:

Units Received: n=1199 (NDA 205-920, eCTD Section 3.2.P.2.2; Performance Evaluation Report QARD-018-11-02 FR , Section 3.1.2, Table 2, pg. 7)

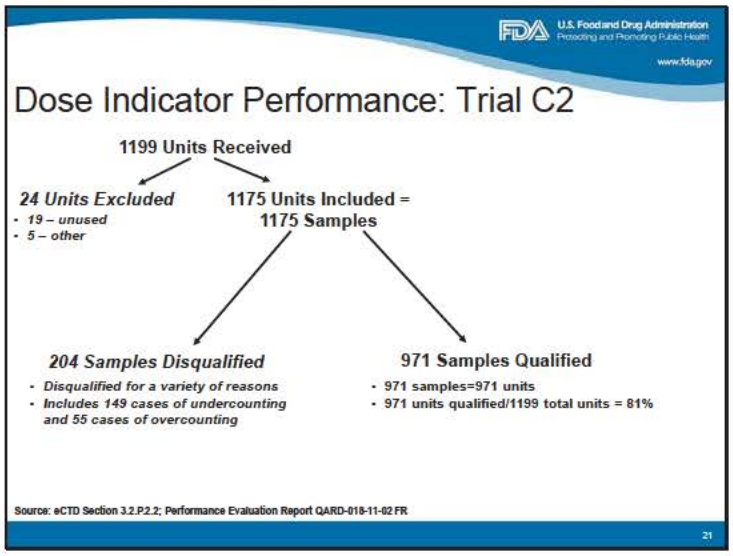
- **Units Excluded: n=24** (Reviewer's calculation 1199-1175=24)
  - **Unused: n=19** (Section 4.3.2, pg. 25)
  - **Other: n=5** (Reviewer's calculation based on data presented on page 25, Section 4.3.2: 2+1+2=5)
- **Units Included: n=1175** (Section 4.3.2, pg. 25); **Samples: n=1175** (Section 4.3.2, pg. 25)
  - **Samples Disqualified: n=204** (Section 4.3.2, Table 27, pg. 29)
    - **Undercounting: n=149** (Section 4.3.2, including Table 24, pg. 26-27)
    - **Overcounting: n=55** (Section 4.3.2, including Table 25, pg. 27-28)
  - **Samples Qualified: n=971** (Section 4.3.2, Table 27, pg. 29)
    - **Samples: n=971 units** (Reviewer's calculation based on data presented on page 25, Section 4.3.2)
    - **Percentage: 81%** (Reviewer's calculation: 971/1199=81%)

Slide 20



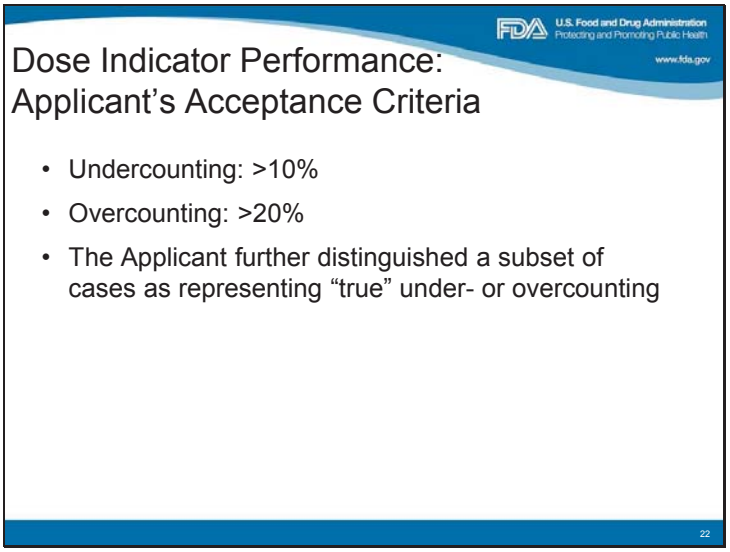
Source: See annotation for Slide 19

Slide 21



Source: See annotation for Slide 19

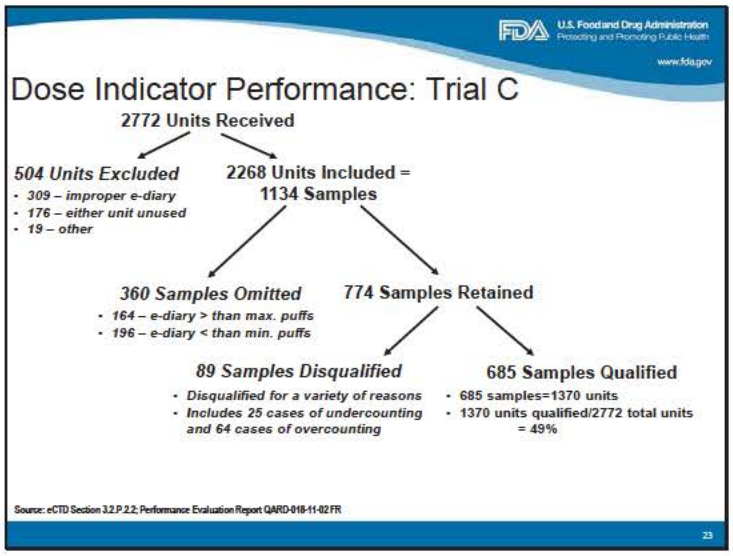
Slide 22



Source:

Applicant's acceptance criteria: >10% for undercounting and >20% for overcounting (NDA 205-920, eCTD Section 3.2.P.2.2; Performance Evaluation Report QARD-018-11-02 FR, Section 3.4, pg. 12)

Slide 23



Source: See annotation for Slide 19.

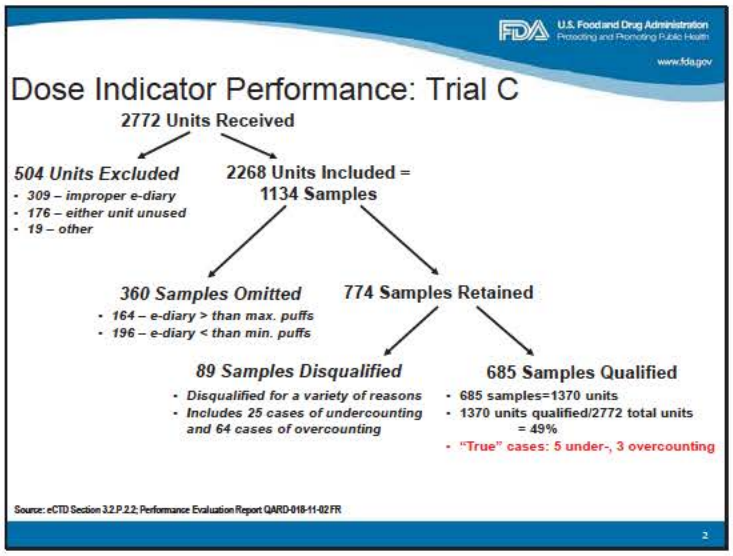
•**Samples Qualified: n=685** (NDA 205-920, eCTD Section 3.2.P.2.2; Performance Evaluation Report QARD-018-11-02 FR , Section 4.3.1.2, Table 22, pg. 24)

- **"True" cases, undercounting: n=5** (Section 4.3.1.2, including Table 22, pg. 20 and 24)
- **"True" cases, overcounting: n=3** (Section 4.3.1.2, including Table 22, pg. 22 and 24)
- **Samples with undercounts <10%: n=240** (Reviewer's calculation based on data presented on page 24, Section 4.3.1.2, Figure 1: 163+77=240)
- **Samples with overcounts <20%: n=437** (Reviewer's calculation based on data presented on page 24, Section 4.3.1.2, Figure 1: 199+118+77+43=437)

•**Samples Disqualified: n=89** (Section 4.3.1.2, Table 22, pg. 24)

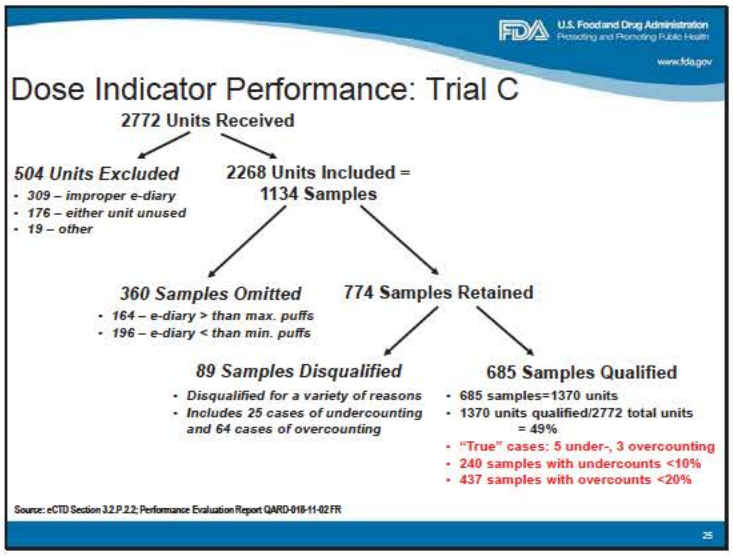
- **Undercounting meeting Applicant's acceptance criteria: n=25** (Section 4.3.1.2, Table 18, pg. 21)
- **Overcounting meeting Applicant's acceptance criteria: n=64** (Section 4.3.1.2, Table 20, pg. 23)

Slide 24



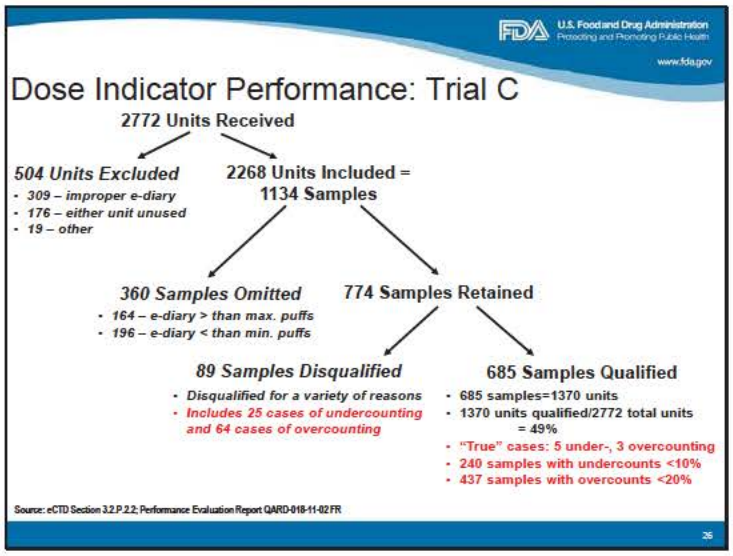
Source: See annotation for Slides 19 and 23

Slide 25



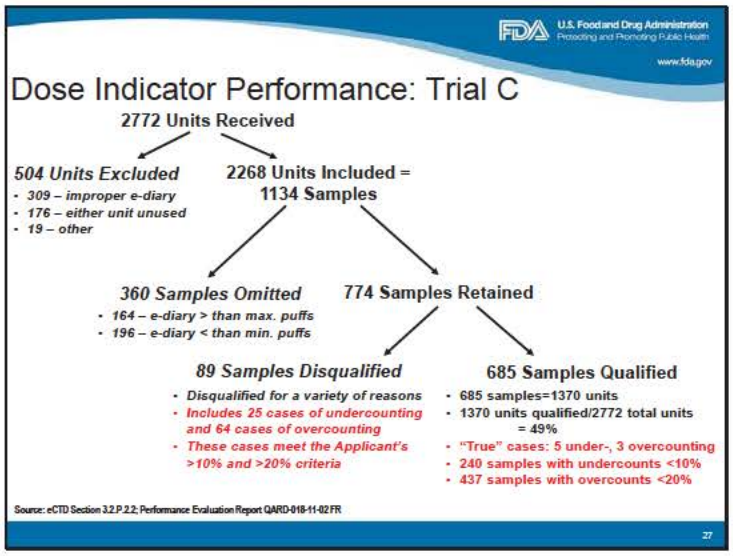
Source: See annotation for Slides 19 and 23

Slide 26



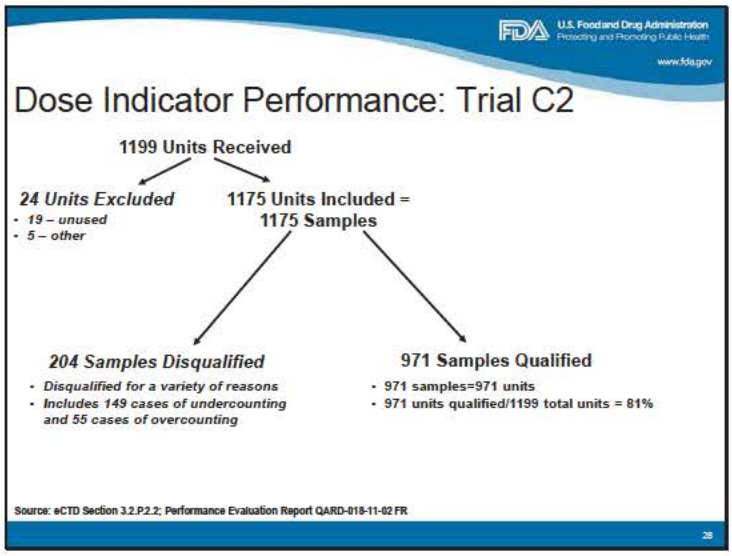
Source: See annotation for Slides 19 and 23

Slide 27



Source: See annotation for Slides 19 and 23

Slide 28



Source: See annotation for Slide 15.

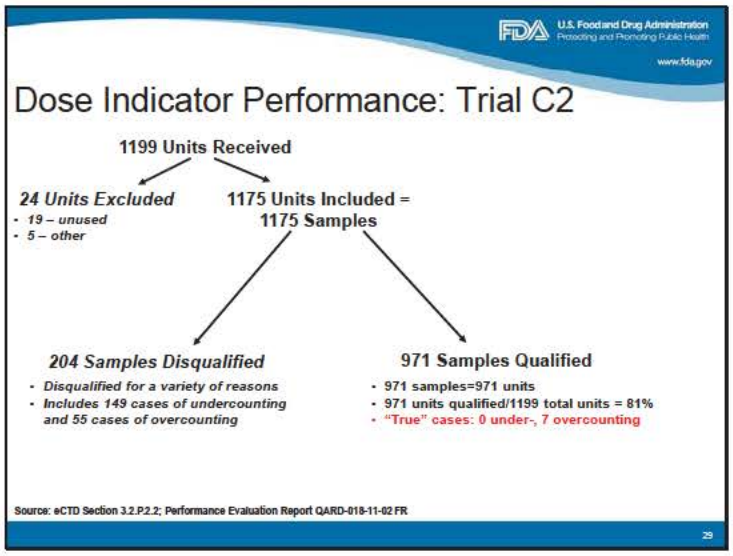
•**Samples Qualified: n=971** (NDA 205-920, eCTD Section 3.2.P.2.2; Performance Evaluation Report QARD-018-11-02 FR , Section 4.3.2, Table 27, pg. 29)

- **"True" cases, undercounting: n=0** (Section 4.3.2, including Table 27, pg. 26 and 29)
- **"True" cases, overcounting: n=7** (Section 4.3.2, including Table 27, pg. 27 and 29)
- **Samples with undercounts <10%: n=362** (Reviewer's calculation based on data presented on page 29, Section 4.3.2, Figure 2: 235+127=362)
- **Samples with overcounts <20%: n=602** (Reviewer's calculation based on data presented on page 29, Section 4.3.2, Figure 2: 375+139+55+33=602)

•**Samples Disqualified: n=204** (Section 4.3.2, Table 27, pg. 29)

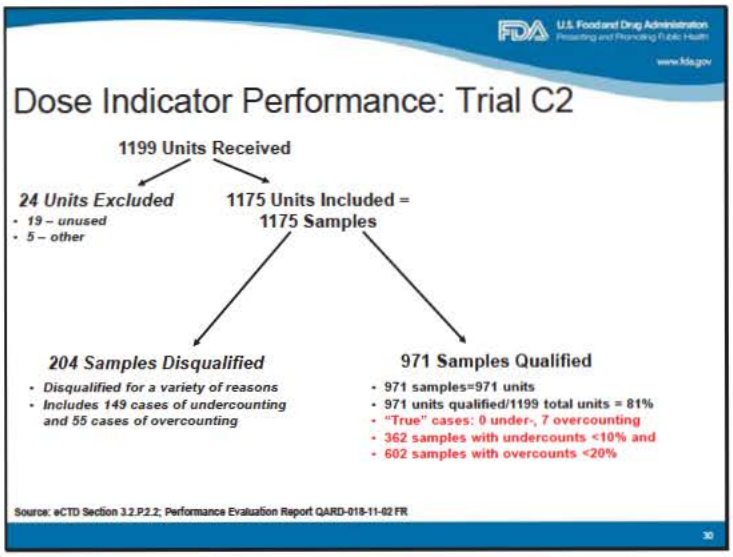
- **Cases of undercounting meeting Applicant's acceptance criteria: n=149** (Section 4.3.2, including Table 24, pg. 26-27)
- **Cases of overcounting meeting Applicant's acceptance criteria: n=55** (Section 4.3.2, including Table 25, pg. 27-28)

Slide 29



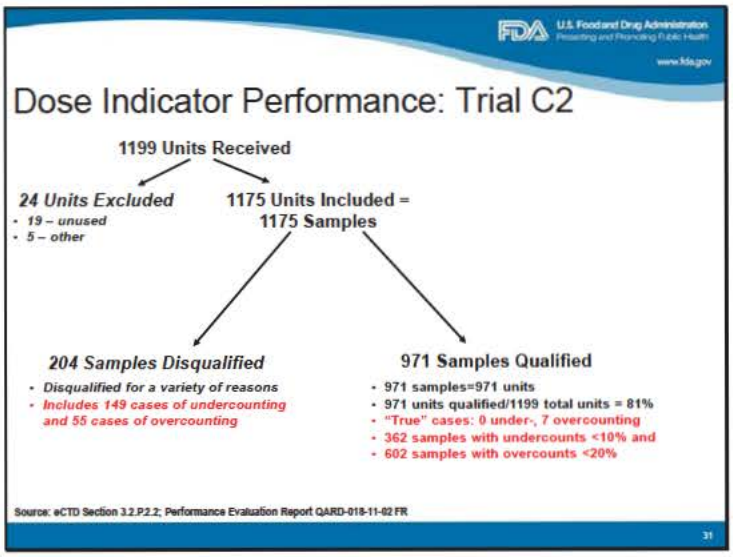
Source: See annotation for Slides 15 and 28.

Slide 30



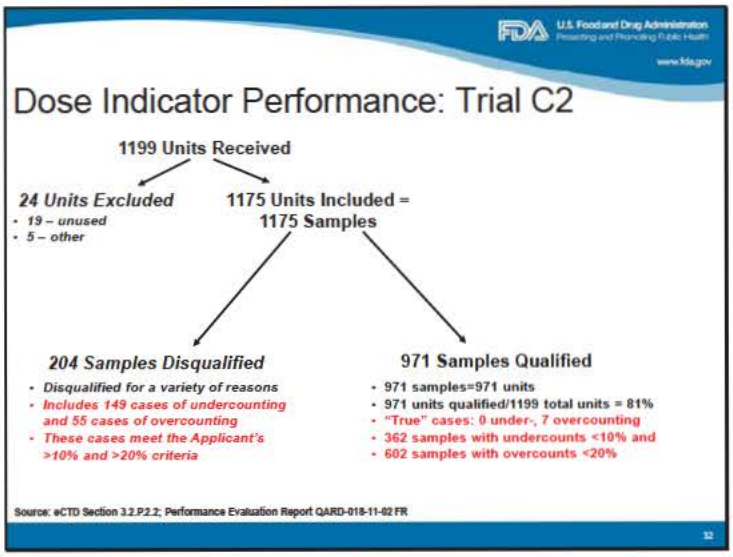
Source: See annotation for Slides 15 and 28.

Slide 31



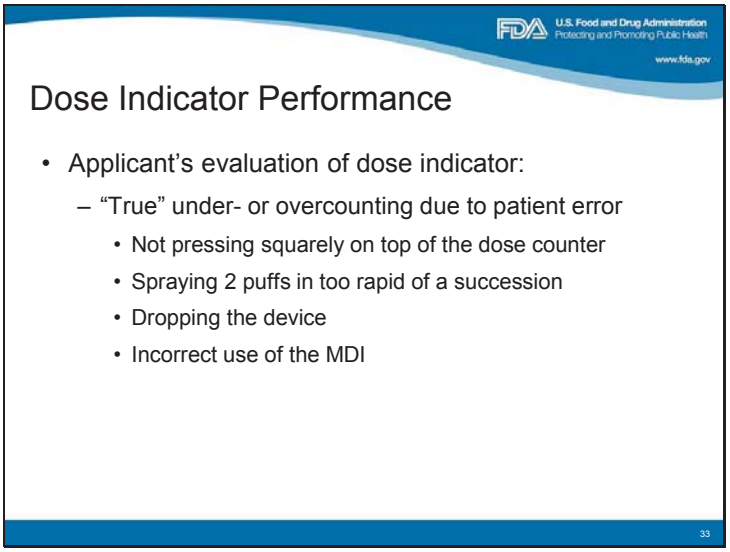
Source: See annotation for Slides 15 and 28.

Slide 32



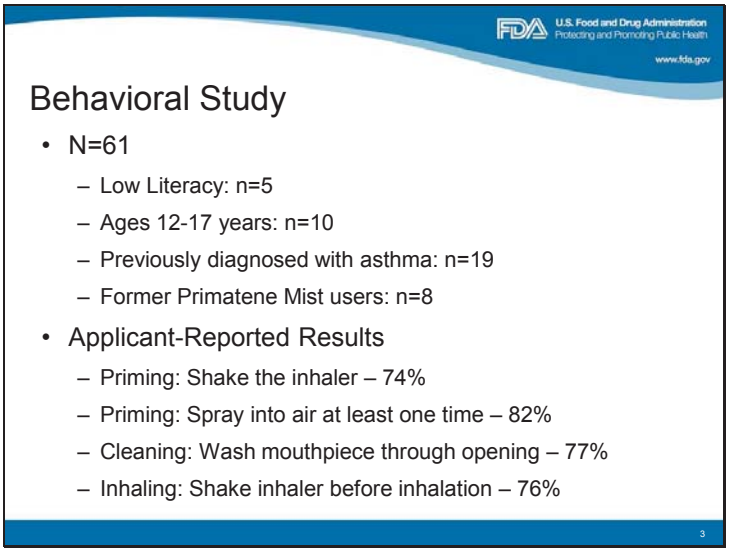
Source: See annotation for Slides 15 and 28.

Slide 33

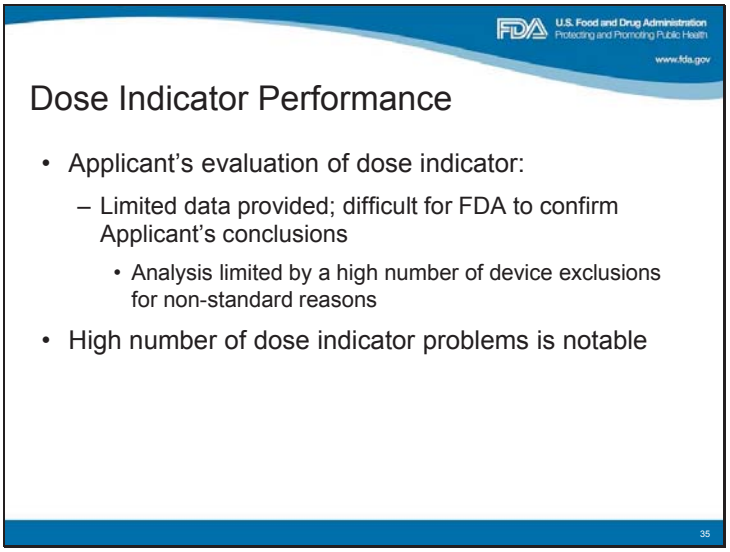


Source: NDA 205-920, eCTD Section 3.2.P.2.2; Performance Evaluation Report QARD-018-11-02 FR , Section 4.3, pg. 20-21 and 26-27

Slide 34

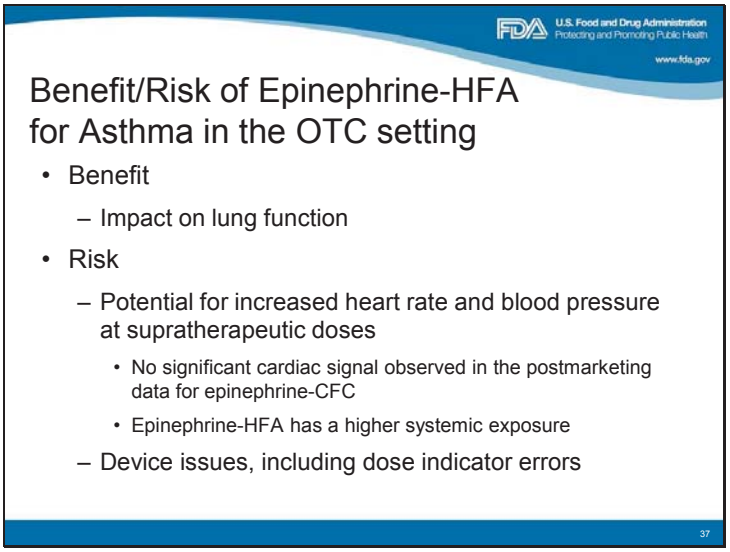


Source: NDA 205-920, eCTD 1.14.1.4, label-behavioral-study-report.pdf, page 23-26 and 31-32


U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov
Dose Indicator Performance
• Applicant's evaluation of dose indicator:
– Limited data provided; difficult for FDA to confirm Applicant's conclusions
• Analysis limited by a high number of device exclusions for non-standard reasons
• High number of dose indicator problems is notable
35

Slide 36


U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov
Agenda
• Device Issues
– Description of Device
– Device Performance
– Dose Indicator Performance
• Benefit/Risk Profile
36


U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov
Benefit/Risk of Epinephrine-HFA for Asthma in the OTC setting
• Benefit
– Impact on lung function
• Risk
– Potential for increased heart rate and blood pressure at supratherapeutic doses
• No significant cardiac signal observed in the postmarketing data for epinephrine-CFC
• Epinephrine-HFA has a higher systemic exposure
– Device issues, including dose indicator errors
37

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN L LIMB
05/21/2014

SALLY M SEYMOUR
05/21/2014

BADRUL A CHOWDHURY
05/21/2014

Labeling Review for

(b) (4)

SUBMISSION DATES:	July 20, 2013 November 5, 2013 December 11, 2013 April 16, 2013 April 18, 2013
NDA/SUBMISSION TYPE:	205920
ACTIVE INGREDIENTS:	Epinephrine HFA 125 mcg/inhalation
DOSAGE FORMS:	Aerosol, metered
SPONSOR:	Armstrong Pharmaceuticals 25 John Road Canton MA 02021 Stephen A. Campbell (909) 942-4176
REVIEWER:	Elaine Abraham RPh
TEAM LEADER:	Steven Adah PhD
PROJECT MANAGER:	Daniel Reed MPH

I. BACKGROUND

NDA 205920 is submitted by Armstrong Pharmaceuticals for (b) (4) (epinephrine HFA 125 mcg/inhalation) aerosol as an OTC rescue inhaler for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. This product replaces the previously approved Primatene Mist with CFC propellant that was removed from the market on December 31, 2011 to comply with the Montreal Protocol.

One labeling issue was included in the 74-day letter sent on October 4, 2013: "Submit annotated font specifications for Drug Facts (See 21 CFR 201.66)." Partial annotated specifications were submitted on November 5, 2013. Another request for the remainder of the specifications with a Drug Facts example was sent by the RPM on April 10, 2014. The

sponsor responded to this request in a submission dated April 18, 2014. However, complete annotated specifications have not been submitted as of the date of this review.

Submitted Labeling	Representative of Following SKUs
160 inhalation canister and carton	N/A
Package insert	N/A

II. REVIEWER'S COMMENTS

A. 160 inhalation canister

i. Outer Carton Label Outside Drug Facts

a. Principal Display Panel (PDP)

1. Trade name

In the July 17, 2013 cover letter, the sponsor states the following in regard to the trade name:

> In February 2013, a Request for Proprietary Name Review was submitted to IND 074286. On July 1, 2013, a teleconference was held between the Agency and Amphastar Pharmaceuticals, Inc., parent company of Armstrong Pharmaceuticals, Inc. Due to the results of that teleconference, the Proprietary Name Review Request has been withdrawn, without prejudice. A final proprietary name has not been selected at this time. The attached labeling reflects the proprietary name (b) (4) however that name may be changed in later versions of the product labeling based on further discussions with the Agency.

The proprietary name (b) (4) and associated labeling was submitted on December 11, 2013. Following the joint Advisory Committee meeting on February 25, 2014 and a teleconference with the Division of Medication Error Prevention and Analysis (DMEPA), the sponsor, submitted a change in the proposed name from (b) (4) to (b) (4) on April 16, 2014 and submitted revised labeling. The trade name (b) (4) is currently under review by DMEPA. If this name is found unacceptable, the sponsor will need to submit revised labeling with a new trade name.

2. Statement of Identity

The statement of identity conforms to 21 CFR 201.61.

3. Net quantity of contents

The PDP contains the statement (b) (4) which is located on the upper half of the PDP. Although this is useful information, it does not conform to 21 CFR 201.62 which states the proper format and location for displaying the net quantity of contents on the PDP. According to § 201.62(a), the declaration of net quantity of contents should be in terms of fluid measure if the drug is a liquid, that is in fluid ounces. We recommend that the corresponding milliliter measure follow the fluid ounce net quantity (see § 201.62(p)). According to § 201.62(e), the declaration of net quantity of

contents shall be placed on the PDP within the bottom 30 percent of the area of the label panel. It is recommended that the number of inhalations in the product be stated on the PDP as this information would be useful to the consumer, but this does not substitute for the net quantity of contents.

4. **Starburst banner**
   What the sponsor calls a "prominent starburst banner" has been added to the lower part of the PDP. The banner states (b) (4) See Important Usage Information on Insert and on Side Panels". The sponsor notes that the starburst will remain on the packaging until a sufficient time has elapsed to ensure that previous users are fully informed of the reformulated product and revised usage information. This banner provides valuable information to the user informing of the change in the product and to read accompanying materials. The banner is acceptable.

b. Top Panel

The April 16, 2014 label submission has revised the top panel which previously contained the trade name and statement of identity information. The revised top panel states the following:

(b) (4)

In general, this information is helpful to the user. The two bullets (b) (4) may not be clear to the user until after reading all of the provided information. We recommend the sponsor clarify these bullets on the top panel.

c. Tamper evident statement

There is no tamper evident statement on the carton label. According to 21 CFR 211.132, each retail package is required to identify all tamper evident features. According to CPG 450.500 Tamper-Resistant Packaging Requirements for Certain Over-the-Counter Human Drug Products and § 211.132, aerosols by design are inherently tamper resistant. Also, § 211.132(c)(1) states that an aerosol that depends on the power of a liquefied or compressed gas to expel the contents does not need a tamper evident statement. The lack of tamper evident statement is acceptable.

d. Expiration date and lot number

The location of the expiration date and lot number must be shown on the outer carton in accordance with 21 CFR 201.17 and 201.18.

ii. Outer Carton Drug Facts Label

a. General

The Drug Facts label was compared to the labeling requirements in 21 CFR 201.66, the bronchodilator labeling in 21 CFR 341.76 and the labeling on the previously approved product (ANDA 87-907).

b. Purpose

The ***Purpose*** title should be right justified rather than right-center justified (see § 201.66(d)(6)).

c. Warnings

1. Asthma Alert

(a) Remove the bullet before the term "**Asthma alert**".

(b) The bulleted statement recommended in the monograph under § 341.76(c) for epinephrine "**see a doctor if you** [bullet] need more than 12 inhalations in 24 hours" has been changed to "…need more than 8 inhalations in 24 hours". As this is allowing fewer inhalations than the monograph labeling, it is acceptable. The monograph bulleted statement "use more than 9 inhalations in 24 hours for 3 or more days a week" has been omitted. This is acceptable from a labeling perspective based on the previous statement in the alert which permits fewer inhalations (8 in 24 hours), but these changes to the **Asthma alert** should be agreed upon by the review team.

(c) Remove the bullet before the statement "These may be signs that your asthma may be getting worse" and end the sentence with a period.

The above changes to the Asthma alert are based on § 341.76(c)(6).

2. Under the subheading, **Do not use**, a period should be placed at the end of the last sentence.

3. Statements listed under **When using this product** follow § 341.76(c) and § 201.66(c)(5)(vi)).

(a) Although the second bulleted statement follows the monograph 21 CFR 341.76(c), the bullet style has been changed in the April 16, 2014 label so that it is hard to differentiate the secondary bullets from the primary bullet. We recommend additional indentation on the secondary bullets to clarify this section as shown below:

When using this product…

- your risk of heart attack or stroke increases if you
  - have a history of high blood pressure or heart disease
  - take this product more frequently or take more than the recommended dose

As currently formatted, these bullets are almost lined up.

(b) There is an additional statement placed in this section – (b) (4)

[redacted]

4. Statements under the subheading **Stop use and ask a doctor if** are acceptable under § 341.76.

d. Directions

1. The bulleted statement [redacted] (b) (4) has been added and is placed on the same line as the ***Directions*** heading. This statement is acceptable but should follow § 201.66(d)(4) so that the bulleted statement is separated from the heading "by at least two square "ems" (i.e. two squares of the size of the letter "M")". Also, the colon following the ***Directions*** heading should be removed.
2. Bolding should be removed from the directions information.
3. We recommend a statement under ***Directions*** informing the consumer to prime before first use.
4. We recommend a statement under ***Directions*** informing the consumer to clean the device daily following use.
5. Because of the number of primary and secondary bullets in this section, the sponsor may want to consider a table for directions for easier reading by the consumer.

e. Other information

1. The heading [redacted] (b) (4) should be changed to the standard Drug Facts heading ***"Other information***" (see § 201.66(c)(7)).
2. The storage conditions have been changed from Primatene Mist CFC [redacted] (b) (4) to "Store at room temperature, between 15-25°C (59-77°F)". According to the CMC review, the temperature range should be [redacted] (b) (4) °C.
3. "Contains no sulfites" statement is acceptable. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people (see 21 CFR 201.22(b)). The CMC reviewer confirmed that the product does not contain sulfites.
4. [redacted] (b) (4) statement is acceptable.

f. Inactive ingredients

The CMC review confirms the ingredient profile and recommends approval. The inactive ingredient section follows § 201.66(c)(8) and is acceptable.

g. Questions or comments?

The information in this section follows § 201.66(c)(9) and is acceptable.
This section should be followed by a barline to conclude the Drug Facts box (see § 201.66(d)(8)).

h. Annotated specifications

1. Several requests for the annotated font specifications have been made of the sponsor. The most recent request made on April 10, 2014 included a Drug Facts sample label showing the specifications needed and a reference to the guidance document describing the specifications. The sponsor responded to this request in a submission dated April 18, 2014 and included two specifications not previously provided. However, complete annotated specifications have not been submitted as of the date of this review. We are aware of the following specifications that have been provided during the course of this review:

Drug Facts heading 9 pt
Drug Facts text 7 pt
Leading 0.5 pt

32 characters per inch

2. The label shows no distinction between barlines and hairlines. Barlines are used to separate the sections described in paragraphs (c)(1) through (c)(9) of § 201.66. According to § 201.66(d)(8), a distinctive horizontal barline extending to each end of the "Drug Facts" box or similar enclosure shall provide separation between each of the headings listed in paragraphs (c)(2) through (c)(9) of this section. The barlines should be extended to the end of the Drug Facts box. The sponsor should refer to the ***Guidance for Industry – Labeling OTC Human Drug Products (Small Entity Compliance Guide) May 2009*** when making changes to the label.

i. Information outside Drug Facts box

1. **Product web site**
   The label contains the statement "See www.primatene.com". This is acceptable until a formal policy is developed by DNCE.
2. (b) (4) **statement**
   In enlarged print is the following statement:
   (b) (4)
   This is acceptable.

iii. Immediate Container labels

a. The bottle label contains reduced labeling information including active and inactive ingredients, use, some warnings, directions and storage conditions. Reduced labeling is acceptable as complete Drug facts are contained on the outer carton (see § 201.66(c)).

b. The label contains the statement (b) (4) This statement should be more explicit informing the consumer to keep insert and carton for complete warnings, instructions and product information.

c. (b) (4)

d. The bolding that is used for some of the words under the heading **Directions** should be removed. The bolded words do not add to consumer understanding.

e. As discussed above, the storage conditions temperature should be changed to (b) (4) .

iv. Package insert

No specific comments will be made on the package insert at this time because it is the subject of the label comprehension studies with recommendations provided by the social scientist. Also, there may be changes to the device which would necessitate changes to the package insert. However, on first glance, the insert could be improved by the following changes. The first section (page) of the insert instructs (b) (4) Up front should be a statement to read all instructions in the insert first. Also the fact that the product has to be primed before first use should be clearly stated upfront but this is found on the second page. A labeling review of the insert will be reserved until after other team member reviews are completed.

III. RECOMMENDATIONS

Issue an Information Request communication to the sponsor for the submitted (b) (4) labeling. These are preliminary comments on the carton and immediate container labels. Recommendations regarding the package insert will be forwarded at a later date. Inform the sponsor that it must make the following labeling revisions:

Outer Carton:

1. **Expiration date and lot number** - The location of the expiration date and lot number must be shown on the outer carton in accordance with 21 CFR 201.17 and 201.18.

Outer Carton Principal Display Panel (PDP):

1. **Net quantity of contents**
   The PDP contains the statement (b) (4) Although this is useful information, it does not conform to 21 CFR 201.62 which states the proper format and location for displaying the net quantity of contents on the PDP. According to § 201.62(a), the declaration of net quantity of contents should be in terms of fluid measure if the drug is a liquid, that is in fluid ounces. We recommend that the corresponding milliliter measure follow the fluid ounce net quantity (see § 201.62(p)). According to § 201.62(e), the declaration of net quantity of contents shall be placed on the PDP within the bottom 30 percent of the area of the label panel. It is recommended that the number of inhalations in the product be stated on the PDP as this information would be useful to the consumer, but this does not substitute for the net quantity of contents.

Outer Carton Top Panel:

1. The two bullets on (b) (4) and (b) (4) may not be clear to the user until after reading all of the provided information. We recommend additional language to clarify these bullets.

Outer Carton Drug Facts Label:

1. ***Purpose***
   The ***Purpose*** title should be right justified rather than right-center justified (see 21 CFR 201.66(d)(6)).
2. **Warnings**
   a. **Asthma Alert** (see 21 CFR 341.76(c)(6))
      - Remove the bullet before the term “Asthma alert”.
      - Remove the bullet before the statement “These may be signs that your asthma may be getting worse” and end the sentence with a period.

   b. Under the subheading, **Do not use**, a period should be placed at the end of the last sentence.

   c. Under **When using this product**, we recommend additional indentation on the secondary bullets to clarify this section as shown below:

When using this product…
- your risk of heart attack or stroke increases if you
  - have a history of high blood pressure or heart disease
  - take this product more frequently or take more than the recommended dose

As currently formatted, these bullets appear almost lined up.

d. Under **When using this product,** the statement [redacted (b) (4)].

3. **Directions**
   a. The bulleted statement [redacted (b) (4)] should follow the ***Directions*** header according to § 201.66(d)(4) so that the bulleted statement is separated from the heading "by at least two square "ems" (i.e. two squares of the size of the letter "M")". Also, the colon following the ***Directions*** heading should be removed.
   b. Bolding should be removed from the directions information.
   c. We recommend as a first statement under ***Directions*** informing the consumer to prime before first use.
   d. We recommend a statement under ***Directions*** informing the consumer to clean the device daily following use.
   e. Because of the number of primary and secondary bullets in this section, the sponsor may want to consider a table for directions for easier reading by the consumer.
4. **Other information**
   a. The heading [redacted (b) (4)] should be changed to the standard Drug Facts heading ***"Other information"*** (see § 201.66(c)(7)).
   b. The temperature range listed for storage should be changed from "15-25°C (59-77°F)" to [redacted (b) (4)]
5. **Questions or comments?**
   This section should be followed by a barline to conclude the Drug Facts box (see § 201.66(d)(8)).
6. **Annotated font specifications for Drug Facts**
   a. Submit complete Drug Facts font specifications. See § 201.66(d) and ***Guidance for Industry – Labeling OTC Human Drug Products (Small Entity Compliance Guide) May 2009***.
   To date, we have received only the following specifications:
   Drug Facts heading 9 pt
   Drug Facts text 7 pt
   Leading 0.5 pt
   32 characters per inch
   If you will being submitting new labeling because of a proprietary name change, complete Drug Facts font specifications should be submitted.

b. The label shows no distinction between barlines and hairlines. Barlines are used to separate the sections described in paragraphs (c)(1) through (c)(9) of § 201.66. Hairlines are used to separate subsections under **Warnings**. According to § 201.66(d)(8), a distinctive horizontal barline extending to each end of the "Drug Facts" box or similar enclosure shall provide separation between each of the headings listed in paragraphs (c)(2) through (c)(9) of this section. Barlines should be extended to the end of the Drug Facts box.

Immediate Container (Bottle) Label for all SKUs

1. The label contains the statement [redacted] (b) (4) This statement should be more explicit informing the consumer to keep insert and carton for complete warnings, instructions and product information.
2. [redacted] (b) (4)
3. The bolding that is used for some of the words under the heading **Directions** should be removed. The bolded words do not add to consumer understanding.
4. As discussed above, the storage conditions temperature should be changed to [redacted] (b) (4)

Package insert

Recommendations regarding changes to the package insert will be forwarded at a later date.

Issue a communication to the sponsor that includes these deficiencies in order to initiate labeling negotiations.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELAINE E ABRAHAM
05/08/2014

STEVEN A ADAH
05/08/2014

FDA Social Science Review: Consumer Studies

Division of Nonprescription Clinical Evaluation (DNCE) Review

Date: April 23, 2014
From: Barbara Cohen, MPA, Social Scientist, DNCE

Through: Lucie Yang, TL, M.D, PhD.
Subject: NDA 205920 – Epinephrine HFA

Executive Summary

The Sponsor conducted four consumer studies in support of this NDA: three sequential label comprehension studies and one behavioral (human factors study). Although upwards of 1400 subjects were studied, no assessments were conducted to determine if subjects knew (without being prompted) to prime the inhaler before using it for the first time, or to clean the inhaler. In general, knowledge about the need to not rely on the dose indicator if the inhaler was dropped, and the need to reprime if not fully dry was not very well understood in label comprehension, and all key relevant subtasks in the general areas of priming and cleaning were not fully demonstrated in the behavioral study. Whether subjects would correctly take an inhalation and adequately reassemble the product for future use was also difficult to assess from the behavioral study. Moreover, the label comprehension study pointed to potential comprehension difficulties concerning indication (specifically only for mild/intermittent asthma) as well as safety concerns and labeled age for use.

Due to the above issues and other methodological concerns with the studies that are discussed in the body of this report, it is recommended that the label be further refined and more rigorously assessed in another LCS (assessing the need to prime and clean in addition to retesting the DFL for other safety concerns). A follow on behavioral study should also be fielded in which subjects are simply asked to envision taking the new inhaler out of the package and using it on Day 1, without any other cuing as to the specific steps that are entailed. Other considerations may involve a scaled down actual use study to assess whether subjects can receive adequate relief from this product, regardless of whether they perform all of the key necessary tasks correctly.

1. Background

Armstrong Pharmaceuticals Inc. (Armstrong) is seeking approval for epinephrine inhalation aerosol hydrofluoroalkane (ephinephrine-HFA) at a dose of 125 mcg/inhalation for over the counter use for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. If approved, epinephrine-HFA would be the only metered dose inhaler (MDI) available for OTC use.

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

Armstrong began interacting with FDA regarding reformulation of epinephrine without CFCs in a pre-IND meeting in 2007 (IND 74286) after publication of the proposed rule. The Agency provided extensive feedback to the Sponsor throughout the development program, including multiple communications outside of traditional milestone meetings.

The four categories of asthma are intermittent, mild persistent, moderate persistent and severe persistent. Classification of asthma based on severity is useful when deciding about management at the initial assessment of a patient. When the patient is already on treatment, asthma severity classification reflects both the severity of the underlying disease and its responsiveness to treatment. Adult and adolescents aged 12 years and older with intermittent asthma are expected to have symptoms two or fewer days per week, nighttime awakenings of two or fewer times per month, use a short acting beta agonist for symptom control two or fewer days per week, have not interference of normal activities by asthma symptoms, have normal baseline lung function, and experience one or fewer exacerbations per year. Although exacerbations can still be severe, SABA taken as needed to treat symptoms is usually sufficient therapy for intermittent asthma.

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

Differences between Epinephrine HFA and CFC:

1. The formulation for epinephrine HFA is a suspension rather than a solution as was for the CFC product. As such, the metered dose inhaler (MDI) must be shaken prior to use to prevent settling.

2. Epinephrine HFA must be cleaned daily to prevent clogging. In contrast, because CFC propellants also function as cleaning agents, daily cleaning was not required in the same way for epinephrine CFC.

3. Epinephrine HFA must be primed prior to first use, if not used in more than 2 days, if still set after cleaning, and if dropped. Priming was not required for epinephrine CFC.

4. Epinephrine HFA contains a dose counter whereas the epinephrine CFC product had a transparent glass reservoir allowing patients to visually determine when the drug solution was running out.

2. Regulatory Activity Regarding Consumer Studies

March 27, 2007:

- (b) (4) FDA responded that because of differences with the counter and the necessity of cleaning the HFA device, the behavior study was needed on the HFA product to determine that consumers can use the device properly. Also, since HFA is a suspension rather than a solution as is the case with the CFC product, special priming instructions may be required.

November 23, 2009 Correspondence:

- The Agency stated that a consumer study or studies may be necessary to determine if the new directions for use can be appropriately followed by consumers. The Agency noted since the proposed product is formulated as a suspension rather than a solution, priming of the device is required for accurate delivery.

October 29, 2010:

- The Agency reminded Amphastar that human factor studies, distinct from the planned Phase 3 trials, as well as CMC in vitro evaluation of device reliability and ruggedness will be required. Amphastar stated that their clinical program would include a robust evaluation of human factors.

November 23, 2010 Correspondence:

- The Agency again reminded Amphastar that the clinical program would need to include a robust evaluation of human factors, demonstration of device ruggedness and assessment of dose counter performance. Amphastar stated that their clinical program would include a robust evaluation of human factors.

September 23, 2011:

- The Agency told the Sponsor to develop proper patient instructions from the results of this study (in vitro testing on cleaning and priming) for cleaning, priming, and repriming – and to evaluate these instructions in a large label comprehension study to determine if they are appropriate for an OTC setting. The Agency also stated that if the directions with regard to administering the drug are not the same as Primatene Mist (e.g., priming, re-priming, cleaning the device and proper dosing which includes the timing of inhalation with respect to timing of actuation), a behavioral use study will be needed to demonstrate that consumers can understand the directions and use the device as specified in the labeling. The Agency noted that the label comprehension study did not need to evaluate all of the elements of a label; it should test only items that differ between the labels for the epinephrine HFA and the epinephrine CFC products, noting that the Agency had not been provided yet with a label for the proposed product. However, the Agency recommended that Amphastar submit the proposed label and a label comprehension study protocol to the Agency for their review and comment.

April 23, 2012 Agency Advice Letter on Previous Draft LCS Protocol and Label:

- Provide the primary and secondary communications objectives to be tested in the label comprehension study.
- Therefore, you should propose a target threshold for success based on a clinical rationale. The labeling aspects (priming, re-priming, dose indicator undercounting) that most need to be tested are not on the Primatene Mist label.
- Ensure that the dose indicator undercounting is one of the primary communications objectives of the study.
- Incorporate the following as communications objectives to be tested:
    - Even though there may be medication in the canister when the dose indicator hits zero, the correct dose in each actuation cannot be assured.
    - One should never try to change the numbers or take the dose indicator off the metal canister.
    - It is recommended to keep track of the number of sprays taken from your inhaler based on your own record.

- Revise the methodology to ensure that low literacy subjects are included, (b) (4) from the sample.
- Include a cohort of Primatene Mist users; they may be accustomed to thinking about usage of the product in a specific way and they need to understand that (b) (4) should be used differently.
- Revise questions that currently can cause framing or mindset bias
- Bring in an independent third party to directly oversee the administration of the written test, rather than Amphastar executives.
- Move the testing venue from Amphastar to another more neutral location.
- Ensure that response choices in multiple choice questions are mutually exclusive and independent and contain only one correct answer.
- When listing response categories for multiple choice submissions, the category "I don't know" should be included as one of the response categories.

January 31, 2013 Type B Meeting Minutes

- The Agency reiterated comments made at the September 2011 meeting that the consumer testing program should include label comprehension and behavioral use studies to ensure that consumers can 1) understand instructions for cleaning, priming and repriming and 2) administer and use the drug product properly. The Agency noted that whether the collected data is sufficient to support the proposed labeling will be a review issue.

June 7 2013 Refuse to File

- NDA 205496 was submitted by the Sponsor on April 6, 2013. From the social science perspective, the NDA could not be reviewed as no accompanying datasets were submitted for the studies. Due to many filing issues (including this one), FDA issued a Refuse to File.

The Sponsor subsequently submitted NDA 205920.

3. Consumer Studies

3.1 Summary Overview of the Consumer Studies

To address FDA's concerns during the reformulated drug development, the Sponsor conducted research and submitted reports for four consumer studies in support of the NDA. Three of these were sequentially conducted, iterative label comprehension studies. In each of the three label comprehension studies there were also "pilot" behavioral studies conducted after the label comprehension component had concluded, involving demonstrations of priming, inhalation and cleaning.

Since the stated purpose of the pilot behavioral studies was to inform procedures to be used in a behavioral study, and since the findings were inevitably biased by the label comprehension that preceded it, pilot results and analysis are not included in this summary report.

There was a standalone behavioral (human factors) study that was conducted after the fielding had concluded for the third label comprehension study. The behavioral study focused on demonstrations of comprehension of key instructions for use – priming, inhalation and cleaning – as had the pilot studies.

Table 1: Summary of Consumer Studies

Study	Dates	N size	Locations
LCS 1	May 21-25, 2012	432	Minnesota, California,Washington State, Florida, Pennsylvania, Georgia, Texas, North Carolina, Utah
LCS 2	June 25-29, 2012	442	Utah, Colorado, Oregon, California, Illinois, New Jersey, Texas, Massachusetts
LCS 3	September 4-14, 2012	471	Texas, Utah, Colorado, California, Arizona, Illinois, Ohio, North Carolina
Behavioral	October 29-November 2, 2012*	61	Utah and California

Note: All interviews of former Primatene users took place at Pegus (CRO) in Salt Lake City
*Source: IR 1/3/14

3.2 Label Comprehension Studies (1, 2 and 3)

Design and Conduct

Study sites were located in retail shopping malls, with the exception of PEGUS. Participants were recruited through foot traffic and did not know at the time of recruitment that the task involved would be reading information on a package of medicine. The survey population consisted of adults and teens, ages 16-17. The REALM test was administered to all participants 18 years of age and over, and the REALM teen test was administered to participants 16 or 17 years of age.

The cohort of consumers who reported use of Primatene Mist in the previous five years was recruited through other means to ensure an adequate number. Social media and other forms of advertisement were utilized to refer potential participants to a 1-800 number to

be screened and to schedule an appointment to complete the interview at a site closest to them. PEGUS interviewed some, but not all, of the former users.

Participants were given the package insert and asked to read it; they were given as much time as needed. The insert remained in front of the participant during the questioning and they could refer to the insert to answer the questions. After the LCS questions were concluded, the interviewer then collected demographic information from participants and asked follow up questions about comprehension questions that were answered incorrectly. (Incorrect responses were flagged by the computerized system and then automatic notification was provided to the interviewer). The purpose of these questions to assess how the label could be improved, and in fact the label was revised between each iteration of the study, as Table 3 illustrates and Appendices 4,5, and 6 indicate.

The studies were conducted with a wide variety of consumers, not just asthma sufferers. Table 2 below – excerpted from the LCS Summary Report - lists the stated specific primary and secondary communication objectives that were tested in the LCS studies, along with the a priori associated target thresholds based on the clinical rationale provided by the Sponsor. (Note: the clinical rationale was not fully provided in the original NDA submission; it was subsequently more comprehensively provided in response to IR #14*)*

Table 2: Primary and Secondary Communications Objectives for LCS Studies

Communication Objective	Safety Risk	Likelihood	Target Level of Comprehension
PRIMARY COMMUNICATION OBJECTIVES			
If the inhaler is dropped, do not rely on the dose indicator. It is recommended to keep track of the number of sprays taken from your inhaler based on your own records.	Low	Minimal	85%
The dose indicator will stop counting at "0" and the inhaler must be replaced.	Low	Moderate	85%
Even though there may be medication in the container when the dose indicator is zero, the correct dose in each spray cannot be assured	Low	Minimal	85%
SECONDARY COMMUNICATION OBJECTIVES			
Never try to change the numbers or take the dose indicator off the metal canister.	Low	Moderate	n/a
The inhaler should be cleaned at the end of the day after use.	Low	Minimal	n/a
Once the red zone appears and the display reads "20", you should obtain a new (b) (4) inhaler soon	Low	Minimal	n/a
You must maintain (reprime) your inhaler under specific circumstances	Low	Minimal	n/a
(b) (4) The number counts down by 20 after you spray 20 times. The number does not count down by 1 each time you spray the inhaler	Low	Minimal	n/a

Source: Sponsor's LCS Summary Report

The stated reason for multiple iterations of the LCS was to retest any primary or secondary objectives that did not do well in previous versions. Prior to retesting, in some instances the Sponsor revised the label wording and graphics. However, in some instances the wording of the questions changed as well, and even the wording of the objectives changed. Table 3 illustrates how, between the iterations of the LCS, wording of the primary and secondary objectives changed, wording of the associated questions changed, and wording/graphics of the associated parts of the label changed. For additional reference, the three labels tested are found in Appendices 1, 2 and 3. The three questionnaires, with answer keys, are found in Appendices 4, 5, and 6.

It's important to keep in mind that the fact that wording and graphics of the label kept changing was a good outcome – the purpose of good label comprehension testing is to make things clearer. The fact that the questions changed over time is more nuanced. For

ease of table interpretation, since the main purpose of this table is to show how objectives and questions changed over time, only the normal literacy point estimates and lower bounds are reported. A more comprehensive table of end of study point estimates and lower bounds is provided in Table 7)

Table 3: Changes in Wording of Communication Objectives and Questions over the Course of LCS 1,2 3 – Together with Descriptions of Label/Graphic Revisions

Primary Communication Objectives	**LCS#**	**Question # and Text**	**Normal Literacy (% correct)**	**Normal Literacy LB**
If the inhaler is dropped, do not rely on the dose indicator. It is recommended to keep track of the number of sprays taken from the inhaler based on your own records.				
If the inhaler is dropped, do not rely on the dose indicator. It is recommended to keep track of the number of sprays taken from your inhaler based on your own records.	1	9. Robert uses Primatene several times a week and usually carries it around with him. This morning he dropped his inhaler in the parking lot, so he reprimed it. Is there anything also that the package insert says Robert should do?	55.6%	50%
Information on what to do if inhaler is dropped was put into a section of its own to make it more visible				
If the inhaler is dropped, do not rely on the dose indicator. Keep track of the number of sprays.	2	10. Robert dropped his inhaler so he cleaned and reprimed it. Is there anything else that the package insert says Robert should do as he uses his inhaler again?	72.6%	67.3%
Information about what to do if inhaler is dropped was emphasized by placing a border around the text.				
If the inhaler is	3	4.What does the package	87.1%	83.1%

dropped, do not rely on the dose indicator. Keep track of the number of sprays.		insert say about the dose indicator if the inhaler is dropped?		
The dose indicator will stop counting at "0" and the inhaler must be replaced.				
The dose indicator will stop counting at "0" and the inhaler must be replaced.	1	10.After using the inhaler, Jen noticed that the dose indicator was zero, but when she shakes the device she can tell there is medicine left in it. What does the package insert say about this?	74.5%	65.4%
Information about the dose indicator was made more prominent by larger graphics, reduced wording and insertion of white space.				
The dose indicator will stop counting at "0" and the inhaler must be replaced.	2	11.After using the inhaler, Jen noticed that the dose indicator was in the red zone and was showing zero, but when she shakes the inhaler it sounds like there is medicine left in it. What does the package insert say about this?	93.1%	89.7%
Even though there may be medication in the container when the dose indicator is zero, the correct dose in each spray cannot be assured.	1	10.After using the inhaler, Jen noticed that the dose indicator was zero, but when she shakes the device she can tell there is medicine left in it. What does the package insert say about this?	74.5%	65.4%
Even though there may be medication in the container when the dose indicator is zero, the correct dose in	2	11.After using the inhaler, Jen noticed that the dose indicator was in the red zone and was showing zero, but when she shakes the inhaler it sounds like	93.1%	89.7%

each spray cannot be assured.		there is medicine left in it. What does the package insert say about this?		
Secondary Objectives:				
Never try to change the numbers or take the dose indicator off the metal canister.				
Never try to change the numbers or take the dose indicator off the metal canister.	1	11.Jean sees that the dose indicator reads zero but she knows there is more medicine in the inhaler so she decides to change the dose indicator to show more sprays. What does the package insert say about this?	77.3%	68.3%
Never try to change the numbers or take the dose indicator off the metal canister.	2	12.Jean decides to change the dose indicator to show more sprays. It did not work so she tried to remove the dose indicator. What does the package insert say about this?	95%	91.9%
The inhaler should be cleaned at the end of the day after use.				
The inhaler should be cleaned at the end of the day after use.	1	1.According to the package insert, when should the mouthpiece be cleaned?	79.5%	74.7%
Cleaning the mouthpiece was revised to reduce the amount of text, additional graphics were added and more white space to make each step stand out.				
The inhaler should be cleaned daily.	2	2.According to the package insert, how often should the mouthpiece be cleaned?	84.2%	79.7%
The mouthpiece	3	5. According to the	96.3%	93.7%

should be cleaned daily		package insert, how often should the mouthpiece be cleaned?		
Once the red zone appears and the display reads "20", you should obtain a new Primatene inhaler soon.				
Once the red zone appears and the display reads "20", you should obtain a new Primatene inhaler soon.	1	6.According to the package insert, what does it mean when the red zone appears on the dose indicator?	96.6%	94%
You must maintain (reprime) your inhaler under specific circumstances				
Reprime your inhaler if you have not used it in more than 2 days, if it must be used before the mouthpiece is dry.	1	2. After cleaning, if the inhaler must be used before the mouthpiece is dry, what should you do before you can use it?	81.4%	76.7%
Reprime your inhaler if you have not used it in more than 2 days, if it must be used before the mouthpiece is dry.	1	8.Sally has not used her inhaler for about a week. What if anything does she need to do to the inhaler before using it again?	86.8%	82.5%
The instructions about priming were revised in a section of their own rather than as part of how to take an inhalation.				
You must prime your inhaler under the following circumstances: If you have not used it in more than 2	2	2.John cleaned his inhaler and it is still wet. Now he must use it before it is dry. What does the insert say he should do?	83.9%	79.6%

days, if you must use it when still wet after cleaning.				
You must prime your inhaler under the following circumstances: If you have not used it in more than 2 days, if you must use it when still wet after cleaning.	2	3.Sally has not used her inhaler for about a week. What, if anything, does she need to do to the inhaler before using it again?	91.9%	87.6%
Sections of priming were revised, when to prime and how many times to spray were consolidated into one place and made more prominent. Reminder added in lower right corner to clean daily; if wet, prime one time.				
You must prime your inhaler under the following circumstances: If you have not used it in more than 2 days, if you must use it when still wet after cleaning.	3	2.John cleaned his inhaler and it is still wet. Now he must use it before it is dry. What does the insert say he should do?	83.9%	79.6%
You must prime your inhaler under the following circumstances: If you have not used it in more than 2 days, if you must use it when still wet after cleaning.	3	3.Sally has not used her inhaler for more than 2 days. What does she need to do to the inhaler before using it again?	91.1%	87.6%
(b) (4) **The number counts down by 20 after you spray 20 times. The number does not count down by 1 each time you spray the inhaler.**				
(b) (6)	1	4. About how many	81.1%	76.3%

(b) (6)		sprays are there in a full inhaler?		
The number counts down by 20 after you spray 20 times. The number does not count down by 1 each time you spray the inhaler.	1	8 Jessica has just started using this inhaler for the first time. She has used two inhalations but noticed that the dose indicator hasn't changed. What does the package insert say about this?	44.1%	38.6%
The dose indicator starts at 160. The number counts down by 20 after you spray 20 times. The number does not count down by 1 each time you spray.	2	4.How do you tell if you have any sprays left in the container?	97.8%	95.5%
The dose indicator starts at 160. The number counts down by 20 after you spray 20 times. The number does not count down by 1 each time you spray.	2	5.About how many sprays are there in a full container?	98.4%	96.4%
The dose indicator starts at 160. The number counts down by 20 after you spray 20 times. The number does not count down by 1 each time you spray.	2	9.How many sprays does it take for the dose indicator to change?	91.5%	87.8%

Source: Integration of various tables in Sponsor's LCS Summary Report

Study Recruitment:

The majority of subjects for all three LCS studies were recruited using direct mall intercept techniques, in which the recruiter approached consumers in the area of the mall around the research site's office. The recruiter first asked the potential participant if they

were willing to participate in a short interview for a specified time period and compensation. No information about the content of the interview was provided. If the person was willing, the prescreening questions were asked and if found qualified, the person was escorted to the research office for the interview. With respect to those who reported previous use of Primatene Mist in the past five years, they were recruited through social media and other advertisements, which referred potential participants to a 1-800 number for initial screening and appointment scheduling at one of the other research sites. Interviews of former Primatene users took place at the Pegus Research Facility in Salt Lake City.

A target sample size of n=470 was specified in each study protocol. Additionally, the protocols specified a target percentage of low literacy participants (25%) as identified by a REALM test score of 60 or less or a REALM-Teen score of 60 or less. The protocol also specified a subgroup of participants with asthma and participants who were former users of Primatene Mist within the past five years (approximately 50 participants). With regard to age:

Table 4: Soft Quotas Used in all Three Studies

Age	%	n
16-17	~3	~15
18-34	~30	~141
35+	~67	~315

For each question in each LCS, the number/percentage of participants who comprehended each communication message was calculated. Correct and (where defined) acceptable response rates were calculated for all participants and also by literacy group and Primatene Mist users vs nonusers. Correct responses were defined as answers that, presented in the consumer's own words, present a complete, ideal answer based on the relevant label statement. Acceptable responses, while less complete, are those that demonstrated participant understanding at a level expected to result in satisfactory compliance under actual use conditions. An incorrect response is defined as a response that indicates that consumers did not understand the corresponding message on the label. Correct and acceptable responses were determined a priori and can be found in the Appendix, Answer Keys and are discussed further in Table 7.

Differences in Communication Objectives Between LCS 1-3

Page 3 of the Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products states that:

All the communication objectives should be identified a priori.

Although these were technically three different label comprehension studies, they were supposed to have been based on the same foundational objectives. Table 3 shows how these objectives were altered slightly over the course of the three studies.

Primary Objectives:

As Table 3 illustrates, the first primary objective was "*If the inhaler is dropped, do not rely on the dose indicator. It is recommended to keep track of the number of sprays taken from your inhaler based on your own records."* However, by the time the LCS 2 was fielded, as Table 3 shows, the second sentence of this objective was edited out to simply read "*Keep track of the number of sprays*." This is a subtle but important difference – initially it was clear that the user needed to keep his/her own records about how many sprays they took, while in the revised objective it was unclear what constituted "keeping track", and how exactly this was supposed to occur.

Likewise, to mirror the revisions to the label in the three studies, the objective regarding cleaning changed throughout the three studies, although in the summary LCS report it is stated as "*the inhaler should be cleaned at the end of each day after use."* This objective was modified for LCS 2: "*the inhaler should be cleaned daily"* and then again for LCS 3: "*the mouthpiece should be cleaned daily."* Although it was probably a good idea to revise in the label and the accompanying objective to clarify that it is the mouthpiece, and not the whole inhaler, that needs to be cleaned, the substitution for "*cleaned at the end of each day after use"* with "*cleaned daily*" is more vague – although again, it reflects the change made to the label. The original objective specified that the inhaler should be cleaned at day's end (when it might have time to air dry overnight before being used again) – and only on days when used. The revised wording implies that there is no difference with respect to what time of day the inhaler is cleaned, and more importantly, also might also imply that it is fine to use this product every day, which is not consistent with the "mild" and "intermittent" labeled indication. Given that many respondents did not understand that the product was to be used for mild or intermittent asthma (see Table 10), this may be a problem.

The dose indicator counting objective also changed slightly from LCS 1 to LCS 2. In LCS 1, the stated objective is (b) (4) *The number counts down by 20 after you spray 20 times. The number does not count down by 1 each time you spray the inhaler.*" The LCS 2 objective begins with: *the dose indicator starts at 160.*" (b) (4) LCS 2 objective (b) (6) that there are only 160 sprays.

Note: Labeling about repriming and the accompanying objectives were also revised throughout the three studies. In the summary LCS, the objective is: *You must maintain (reprime) your inhaler under specific circumstances.* In LCS 1, the objective was *"reprime your inhaler if you have not used in more than two days, if it must be used before the mouthpiece is dry."* In LCS 2, the objective was changed to read "*You must*

prime your inhaler under the following circumstances: If you have not used in more than two days, if you must use it when still wet after cleaning." However, since this revised wording of the objective did not have an accompanying change in meaning, I consider it to be acceptable.

Questions/How the Questions Changed from LCS 1 to LCS 3

Another methodological issue of concern is that two of the three primary communications objectives in this study were measured by a single scenario question (with the wording of the question changing from LCS 1 to LCS 2):

- *The dose indicator will stop counting at 0 and the inhaler must be replaced*
- *Even though there may be medication in the container when the dose indicator is 0, the correct dose in each spray cannot be assured.*

This is not in accordance with the Label Comprehension Guidance, which states on page *"Questions should be direct, specific, and unambiguous. Each question should address a single item or issue."*

The wording of the relevant scenario question in LCS 2 was (this objective was not tested in LCS 3 as it was determined to be sufficiently comprehended):

After using the inhaler, Jen noticed that the dose indicator was in the red zone and was showing zero, but when she shakes the inhaler it sounds like there is medicine left in it. What does the package insert say about this?

As the answer key (Appendix 5 states), the Sponsor characterized this question as answered correctly if *either* of the items below was checked:

- The inhaler must be replaced/stop using/throw away
- The correct dose cannot be assured.

In other words, if either of the items below was checked, the Sponsor determined that both primary objectives were understood.

In responding to the question, some respondents thought about the fact that even though there was medicine left, the correct dosage could not be assured, and some respondents thought about the fact that the dose indicator was showing zero and so the inhaler needed to be replaced. Depending on how they interpreted the question, they generally gave an answer that addressed the interpretation. The Sponsor then summed up the correct answers for one interpretation and the correct answers for the other interpretation, minus the overlap of those who answered in a way that covered both interpretations; therefore the overall "correct" score of the entire question was answered and applied to each of the objectives it was trying to assess.

Table 5: LCS Study 2 – Question 11: % respondents who gave each response.

Response Category	% Correct	95% CI
Inhaler must be replaced/stop using/throw away	61.8% (273/442)	57.0-66.3
The correct dose cannot be assured	48.2% (213/442)	43.4-53.0

Source: Behavioral Statistics

Table 6: LCS Study 2 Question 11: % respondents who mentioned both key objectives in their answer

Inhaler must be replaced/stop using/throw away	The correct dose cannot be assured	
	Mentioned	Did not mention
Mentioned	87 (19.7%)	186 (42.1%)
Did not mention	126 (28.5%)	43 (9.7%)

Source: Behavioral Statistics

In a sense, the Sponsor could argue that most respondents understood that either way, there was a problem with the inhaler. Therefore, it was acceptable to report out the data this way. However, I still believe that it was misleading.

As an example of the issue that I find with this approach, if someone responded that the correct dose could not be assured, I believe that that response affirmed an understanding of primary objective 3 but not of primary objective 2. Theoretically, someone could decide to take their chances about the correct dosing but still not completely understand that the inhaler needed to be replaced. Therefore, I do not agree with the Sponsor's answer key or definition of correct response, given that this question embodied not one but two key objectives. Moreover, the sponsor characterized the response "the dose indicator will stop counting at zero" as acceptable. This response does not reflect comprehension of either objective – someone could merely interpret that to mean that the dose indicator was problematic and not that there wasn't any medicine left.

Secondary Objectives:

Regarding the secondary objective of "*never try to change the numbers or take the dose indicator off of the metal canister*" - the question in LCS 2 was biased in that (unlike LCS 1), it did not provide a reasonable explanation as to why someone would want to change the dose indicator and thus inherently cued that the action was unreasonable. Moreover, this is a double barreled objective, with two different subparts – one about not changing

numbers, and one about not taking the indicator off. The answer key reveals that in addition to both "*never change the numbers" and "never take the dose indicator off*" being considered correct, the mention of either without the other was also considered acceptable. Thus, respondents did not have to understand both aspects of this objective to get it correct.

Regarding the re-priming secondary objective, here it was also double barreled objective also but instead there were two questions used to measure two subparts; each question focused on a different aspect of the objective. Therefore, that aspect of the questions was acceptable. Of interest however, when the scenario of not having used the inhaler for a week (LCS 1 and 2) was used, respondents were not as likely to respond as correctly as when the scenario of not having used it for two days (LCS 3) was used. Since "*two days*" was the exact time period mentioned on the label, it seems as if respondents had trouble applying this aspect of the label to a different circumstance other than what was literally on the label. Moreover, the question in LCS 3 deleted the phrase *"if anything*" from "*what if anything does she need to do…."* With the deletion of this phrase, respondents were cued that was an action that needed to be taken and therefore may have been more prompted to reexamine the label if they didn't recall what it was.

Finally, regarding the secondary objective of the dose indicator starting at 160 and counting down by increments of 20, it's unclear why the question "How do you tell if you have any sprays left in the container" was included as part of the comprehension assessment of that objective. In fact, in LCS 1, it was included as merely an informational question along with many other questions (see Appendix 4).

Below is a table of final results for normal and low literates, as well as former Primatene users vs non-users. Comprehension is also broken out into correct and acceptable, where relevant.

Table 7– Sponsor Reported Final Results

Primary Communication Objective	Question	Normal Literacy	Low Literacy	Former Primatene Mist Users	Non Users	Total
		% Correct	% Correct	%Correct	%Correct	%Correct
If the inhaler is dropped, do not rely on the dose indicator. Keep track of the number of sprays.	Study 3: Q4. What does the package insert say about the dose indicator if the inhaler is dropped?	87.1% N=348 83.1%-90.4% Total Correct: 219 (62.9%) Total Acceptable: 84 (24.1%)	72.1% N=122 63.3%-79.9% Total Correct: 56 (45.9%) Total Acceptable: 32 (26.2%)	74.2% N=62 61.5%-84.5% Total Correct: 39(62.9%) Total Acceptable: 7 (11.3%)	85.0% N=406 81.1%-88.3% Total Correct: 236 (58.1%) Total Acceptable: 109 (26.8%)	83% N=471 79.3%-86.3% Total Correct: 275(58.4%) Total Acceptable: 116 (24.6%)
The dose indicator will stop counting at "0" and the inhaler must be replaced.	Study 2: Q11. After using the inhaler, Jen noticed that the dose indicator was in the red zone and was showing zero, but when she shakes the inhaler it sounds like there is medicine left in	93.1% N=317 89.7%-95.6%	88.8% N=125 81.9%-93.7%	90% N=100 82.4%-95.1%	92.4% N=342 89.1%-95%	91.9% N=442 88.9%-94.2%

	it. What does the package insert say about this?					
Even though there may be medication in the container when the dose indicator is zero, the correct dose in each spray cannot be assured.		93.1% N=317 89.7%-95.6%	88.8% N=125 81.9%-93.7%	90% N=100 82.4%-95.1%	92.4% N=342 89.1%-95%	91.9% N=442 88.9%-94.2%
Never try to change the numbers or take the dose indicator off the metal canister.	Study 2: Q.12. Jean decides to change the dose indicator to show more sprays. It did not work so she tried to remove the dose indicator. What does the package insert say about this?	95% N=317 91.9%=97.1% Total Correct: 144 (45.4%) Total Acceptable: 157 (40.5%)	88.8% N=125 81.9%-93.7% Total Correct: 44 (35.2%) Total Acceptable: 67 (53.6%)	96% N=100 90.1%-98.9% Total Correct: 44 (44%) Total Acceptable: 52 (52%)	92.4% N=342 89.1%-95% Total Correct: 144 (42.1%) Total Acceptable: 172 (50.3%)	93.2% N=442 90.5%-95.4% Total Correct: 188 (42.5%) Total Acceptable: 224 (50.7%)

The mouthpiece should be cleaned daily.	LCS 3: Q5. According to the package insert, how often should the mouthpiece be cleaned?	96.3% N=348 93.7%-98%	88.5% N=122 81.5%-93.6%	95.2% N=62 86.5%-99%	94.6% N=406 91.9%-96.6%	94.1% N=471 91.5%-96%
Once the red zone appears and the display reads “20”, you should buy a new Primatene inhaler soon.	LCS 2: Q7. According to the package insert, what does it mean when the red zone appears on the dose indicator?	100% N=317 100-120%	98.4% N=125 94.3%-99.3%	100% N=100	99.4% N=342 97.9%-99.9%	99.5% N=442 98.4%-99.9%
You must prime your inhaler under the following circumstances: If you have not used it in more than 2 days; if you must use it when still wet after cleaning.	LCS 3: Q2. John cleaned his inhaler and it was still wet. Now he must use it before it is dry. What does the insert say he should do?	83.9% N=348 79.6%-87.6%	75.4% N=122 67.7%-83.5%	75.8% N=62 80.1%-96.4%	83% N=406 83.5%-90.3%	81.5% N=471 83.7%-89.9%
	Q.3. Sally has not used her inhaler for more	91.1% N=348	76.2% N=122	90.3% N=62	87.2% N=406	87% N=471

	than two days. What does she need to do to the inhaler before using it again?	87.6%-93.9%	67.7%-83.5%	80.1%-96.4%	83.5%-90.3%	83.7%-89.9%
The dose indicator starts at 160. The number counts down by 20 after you spray 20 times. The number does not count down by 1 each time you spray the inhaler.	LCS 2: Q4. How do you tell if you have any sprays left in the container?	97.8% N=317 95.5%-99.1% Total Correct: 283 (89.3%) Total Acceptable: 27(8.5%)	84% N=125 76.4%-89.9% Total Correct: 89 (71.2%) Total Acceptable: 16 (12.8%)	97% N=100 91.5%-99.4% Total Correct: 86 (86.0) Total Acceptable:11(11%)	93% N=342 89.7%-95.5% Total Correct: 286 (83.6%0 Total Acceptable: 32 (9.4%)	93.9% N=442 91.2%-95.9% Total Correct: 372 (84.2%) Total Acceptable: 43 (9.7%) 96.6%
	Q.5. About how many sprays are there in a full container?	98.4% N=317 96.4%-99.5%	92% N=125 85.8%-96.1%	96% N=100 90.1%-98.9%	96.8% N=342 94.3%-98.4%	96.6% N=442 94.5%-98.1%
	Q.9. How many sprays does it take for the dose indicator to change?	91.5% N=317 87.8%-94.3%	72% N=125 63.3%-79.7%	87% N=100 78.8%-92.9%	85.7% N=342 81.5%-89.2%	86% N=442 82.4%-89.1%

Analysis of Overall Sponsor Reported Findings

Within the context of the above caveats, which quite possibly served to upwardly bias the findings of this study, below are some of the key results, as reported out in Table 7 above. Table 7 displays the final comprehension scores for each primary and secondary objective and notes in which of the three LCS studies these scores were reported from:

1. Primary Objective 1: *If the inhaler is dropped, do not rely on the dose indicator*, was problematic for respondents to understand. Even on the third iteration of the label and questionnaire (LCS 3), this did not meet the lower bound (LB 83.1%) for normal literacy.

    a. Low literacy respondents were even more problematic; here, as Table 9 illustrates, 72.1%, 63.3% LB. For total combined respondents, 83.9%, 79.1% LB.

    b. Non Primatene users were directionally more likely to understand than Primatene users.

2. Primary Objectives 2 and 3: *The dose indicator will stop counting at "0" and the inhaler must be replaced and*

3. *Even though there may be medication in the container when the dose indicator is zero, the correct dose in each spray cannot be assured*.

    These met the lower bounds but as discussed above, were measured by the same question and therefore the validity is open to question.

As for the secondary objectives, again, within the context of the above caveats, they scored relatively well among normal literacy (all were above 85% by LCS 3)

    a. Regarding the need to re-prime when still wet after cleaning, at 79.6 LB% for normal literacy, (67.7% LB LL) this was problematic.

    b. Regarding the need to re-prime after not having used the product for two days or more, although comprehension of this was acceptable for normal literates (87.6% LB), it was still not good among low literates (67.7% LB)

Additional Findings (Not Primary or Secondary Objectives) in LCS 2

LCS 2 posed two "informational" questions that had not been asked in LCS 1. LCS 3 followed up with a second iteration of the initial priming question.

Although it was a good idea to include a question about initial priming, it would have been far better to have posed an open ended, unaided question about what if anything needed to be done

before using the product for the first time. Instead, the question assumed the knowledge of the need to prime and instead merely asked about the number of sprays involved. As it was, this question was very directive and also probably significantly helped to bring respondents' focus to the section of the reworked label that dealt with other situations in which to prime, so as to be in an optimal position to correctly respond to the reworked questions that were in fact a priori communications objectives regarding priming. The need to prime before using the inhaler for the first time should also have been a primary or secondary objective.

Table 8: Informational Objectives in LCS 2 - % Correct

Communication Message	Question # and Text	Normal Literacy (95% CI) N=317	Low Literacy (95% CI) N=125	Users (95% CI) N=100	Non-Users (95% CI) N=341	Total (95% CI) N=442
Before you use the inhaler for the first time, you must prime it four (4) times to get the right amount of medicine.	**Question 1:** *According to the package insert, how many times do you need to prime the inhaler before you use it for the first time?*	94% (90.8%, 96.4%)	80% (71.9%, 86.6%)	89% (81.2%, 94.4%)	90.4% (86.7%, 93.3%)	**90% (86.9%, 92.7%)**
The dose indicator shows how many sprays you have left	**Question 6:** *What does the dose indicator do?*	98.4% (96.4%, 99.5%)	84.8% (77.3%, 90.6%)	98% (93.0%, 99.8%)	93.6% (90.4%, 95.9%)	**94.6% (92.0%, 96.5%)**

Source: Sponsor's LCS 2 Report

Table 9: Informational Objective in LCS 3 - % Correct

Communication Message	Question # and Text	Normal Literacy (95% CI) N=348	Low Literacy (95% CI) N=122	Users (95%CI) N=62	Non-Users (95% CI) N=406	Total (95%CI) N=471
Before you use the inhaler for the first time, you must prime it four (4) times to get the right amount of medicine.	Question 1: According to the package insert, how many times do you need to prime the inhaler before	97.4% (95.1%, 98.8%)	90.2% (83.4%, 94.8%)	91.9% (82.2%, 97.3%)	96.6% (94.3%, 98.1%)	95.3% (93.0%, 97.0%)

	using it for the first time?					

Source: Sponsor's LCS 3 Report

Additional "Informational" Objectives (Not Primary or Secondary Objectives) in LCS 1

LCS 1 included 14 other questions that were characterized by the Sponsor as "informational" – neither primary nor secondary objectives – and therefore were not included in subsequent LCS iterations.

Table 10: Informational Questions in LCS 1 - % Correct

Other Information	Question # and Text	Low Literacy (95% CI) N=110	Normal Literacy (95% CI) N=322	Users (95% CI) N=71	Non-Users (95% CI) N=361	Total (95% CI) N=432
1. How do you tell how many sprays are left?	**Question 3:** *How do you tell how many sprays you have left in the inhaler?*	71.8%% (62.4%, 80.0%)	89.4% (85.6%, 92.6%)	87.3% (77.3%, 94.0%)	84.5% (80.3%, 88.1%)	**85.0% (81.2%, 88.2%)**
2. What does the dose indicator do?	**Question 5:** *What does the dose indicator do?*	88.2% (80.6%, 93.6%)	94.1% (90.9%, 96.4%)	90.1% (80.7%, 95.9%)	93.1% (89.9%, 95.5%)	**92.6% (89.7%, 94.9%)**
3. What is this product used for? (Asthma)	**Question 12:** *What is this product used for?*	81.8%	93.8%	90.1%	90.9%	**90.7%**
4. What is this product used for? (Mild and intermittent symptoms of Asthma)	**Question 12A:** *What type of Asthma does it treat?*	56.4% (46.6%, 65.8%)	75.2% (70.1%, 79.8%)	47.9% (35.9%, 60.1%)	74.8% (70%, 79.2%)	**70.4% (65.8%, 74.6%)**
5. Asthma Alert Warnings Sign of worsening asthma	**Question 13:** *There are several warnings under the Asthma Alert. If any of these conditions happen, what might this be a sign of?*	54.5% (44.8%, 64.1%)	67.4% (62.0%, 72.5%)	63.4% (51.1%, 74.5%)	64.3% (59.1%, 69.2%)	**64.1% (59.4%, 68.6%)**
6. Risks of using this	**Question 14:** *According to the*	87.3%	96.0%	97.2%	93.1%	**93.8%**

product	*"When using this product" section of the label, what are some of the risks associated with this product?*	79.6%, 92.9%)	(93.2%, 97.8%)	(90.2%, 99.7%)	(89.9%, 95.5%)	**(91.0%, 95.8%)**
7. What may increase risk of heart attack or stroke when using this product	**Question 15:** *According to the label, what are the things that may increase the risk of heart attack or stroke when using this product?*	49.1% (39.4%, 58.8%)	70.2% (64.9%, 75.1%)	69% (56.9%, 79.5%)	64% (58.8%, 68.9%)	**64.8%** **(60.1%, 69.3%)**
8. Action to take if have 4 asthma attacks in one week	**Question 16:** *Camille has had 4 asthma attacks in one week. According to the label, what should Camille do?*	91.8% (85.0%, 96.2%)	93.8% (90.6%, 96.2%)	97.2% (90.2%, 99.7%)	92.5% (89.3%, 95%)	**93.3%** **(90.5%, 95.5%)**
9. Heart beats faster when using this product action to take	**Question 17:** *Jay has been using this product for his asthma. Sometimes he notices that his heart beats faster than usual. According to the label, what should Jay do?*	82.7% (74.3%, 89.3%)	87.9% (83.8%, 91.2%)	80.3% (69.1%, 88.8%)	87.8% (84%, 91%)	**86.6%** **(83.0%, 89.6%)**
10. Action to take when using this product and having difficulty sleeping	**Question 18:** *Jayne has been using Primatene to treat her asthma symptoms for a few months. She has noticed recently that she has difficulty sleeping. What does the label say Jayne should do?*	94.5% (88.5%, 98.0%)	96.0% (93.2%, 97.8%)	94.4% (86.2%, 98.4%)	95.8% (93.2%, 97.7%)	**95.6%** **(93.2%, 97.3%)**
11. Number of inhalations in each dose	**Question 19:** *For adults and children 4 years of age and older, according to the label how many*	88.2% (80.6%, 93.6%)	96.6% (94.0%, 98.3%)	95.8% (88.1%, 99.1%)	94.2% (91.2%, 96.4%)	**94.4%** **(91.8%, 96.4%)**

	inhalations is in a dose?					
12. Waiting to dose action to take after two doses – wait four hours	**Question 20:** *Charlotte took one inhalation and waited for a minute. Her asthma symptoms were not relieved so she took another inhalation. How long should she wait to use Primatene again?*	80.9% (72.3%, 87.8%)	90.1% (86.3%, 93.1%)	88.7% (79%, 95%)	87.5% (83.7%, 90.8%)	**87.7%** **(84.3%, 90.7%)**
13. Maximum doses in a 24 hour period	**Question 21:** *According to the label, what is the maximum number of inhalations a person should use in a 24 hour period?*	90.9% (83.9%, 95.6%)	98.1% (96.0%, 99.3%)	98.6% (92.4%, 100%)	95.8% (93.2%, 97.7%)	**96.3%** **(94.1%, 97.9%)**
14. Dosing direction if under age 4	**Question 22:** *Megan has a 3 year old son who has asthma. What instructions does the label give Megan about giving this medicine to her son?*	68.2% (58.6%, 76.7%)	83.5% (79.0, 87.4%)	77.5% (66%, 86.5%)	80.1% (75.6%, 84.1%)	**79.6%** **(75.5%, 83.3%)**

Of note were comprehension issues on several questions:

- Q 12a – What type of asthma does it treat?: (Correct answer: mild or intermittent)
  - 75.2% NL (70.1%LB), 56.4% LL (46.6%LB)

- Q 13 – There are several warnings under the Asthma Alert. If any of these conditions happen, what might this be a sign of? (Correct answer: Your asthma may be getting worse)
  - 67.4%NL (62%LB), 54.4%LL (44.8%LB)

- Q15 – According to the label, what are the things that may increase the risk of heart attack or stroke when using this product? (Correct answer: any two of the following: history of high blood pressure, history of heart disease, taking this product more often than directed, taking more than the recommended dose, Acceptable answer: any one of the above)
  - 70.2%NL (64.9%LB); 49.1%LL (39.4%LB)

- Q22 – Megan has a 3 year old son who has asthma. What instructions does the label give Megan about giving this medicine to her son? (Correct answer: ask a doctor)
    - 83.5%NL (79%LB); 68.2%LL (58.6% LB)

  Of note, the scenario of a three year old using the product would not have been appropriate under the former Primatene CFC labeling either, since age four was the minimum labeled age. Therefore, this question did not adequately assess comprehension of differences in the label between the two formulations.

- Q20 - Charlotte took one inhalation and waited for a minute. Her asthma symptoms were not relieved so she took another inhalation. How long should she wait to use Primatene again? (Correct answer: 4 hours)
    - 90.1%NL (86.3%LB) vs 80.9%LL (72.3% LB)

The Sponsor maintains that as these are monograph statements, they do not need to be rigorously assessed in label comprehension. Although the Agency maintains that commonly used labeling statements typically do not need to be retested, there are exceptions if it is believed that for a specific product, it is important that they be assessed. When the Agency was in reformulation development discussions with the Sponsor, the revised labeling was not yet available. Unfortunately, as discussed earlier, the cohort of former Primatene users was inexplicably missing from LCS 1, the only LCS in which these and other statements were tested. If there is concern that former Primatene users may not choose to read the DFL because they may think they are already familiar with the product dosing and warnings, then it may be worthwhile to ask for additional testing on this.

Additional FDA Perspectives

The Agency's April 23 2012 Advice Letter – based on a previous protocol of an earlier LCS submitted for feedback - discussed target success thresholds within the context of clinical rationale, stated that the label aspects that most needed to be tested were priming, repriming and dose indicator undercounting. Additionally, the Agency specifically mentioned that ensuring that dose indicator undercounting was understood should be one of the primary communications objectives of the study. The Sponsor did not adhere to this advice, as dose indicator undercounting was mostly a secondary, and not primary, objective.

Also not included in label comprehension testing was an assessment of what exact actions (e.g., shaking and spraying into the air) priming and re-priming were comprised of. This is an example of where a clearer label based on a good LCS might have helped achieve better results in the follow on behavioral study.

3.3 Behavioral Study

Objectives

The objectives of the behavioral study were to determine if participants were able to adequately demonstrate:

- How to prime the inhaler
- How to clean the mouthpiece
- How to reassemble the inhaler
- How to correctly place their finger on the canister/dose indicator to actuate the inhaler
- How to dose with the inhaler.

Study Design and Conduct

This study was conducted with 61 subjects at the Salt Lake City research facility of Pegus, and a consumer research facility in Montclair, California. Subjects were recruited through poster and flyer advertisements, social media recruitment tools and a purchased database of asthma sufferers.

Of the 61 subjects, 19 were asthma sufferers and 8 had reported use of Primatene within the previous 5 years. Additionally, five participants were assessed as low literate. The percentage of both former Primatene users and low literates was too low to be able to draw even qualitative inferences regarding increased likelihood of difficulties (or not) for these subgroups. This was an important drawback of the study, particularly given the concerns that FDA had expressed to the Sponsor during the reformulated drug development.

There were also ten participants ages 12-17. In the case of the children, a parent or guardian was required to accompany any subject under the age of 16, and it was left up to the parent to decide on how much they coached the child on steps needed for proper care and use of the product. However, the child was required to demonstrate the steps to actually use the product with or without help from the parent, as it was thought that a parent would not always be present when the child needed to dose with Primatene.

For the study, subjects were shown the package insert and asked to read it. They were then informed that they would be asked to demonstrate some of the procedures described in the package insert. Of note, subjects were asked to familiarize themselves with the (b) (4) inhaler prior to the actual demonstration that was videotaped and that served as the basis for scoring. Although according to the Sponsor, the interviewers were not permitted to respond during this time to any of the questions from participants about how to use the product or about any of the instructions, it's important to keep in mind that subjects appeared to have as much time as they needed to familiarize themselves before being "tested" with the camera on. It's unclear whether that would happen in a real life situation during an asthma attack.

Also of note was that there was no sink available to the subjects to demonstrate washing. The Sponsor asserts that choosing to have subjects pantomime the steps required them to think through the procedures themselves rather than being overly prompted to do this by being led to an area by a sink.

While a review of 20 of the videotapes showed that they were still able to reasonably pantomime the act of washing both ends of the mouthpiece when subjects understood this direction, the necessity of doing so for 30 seconds on each end, with warm water, was not able to be demonstrated adequately through pantomime. Therefore, the interviewers in many instances needed to prompt the subjects through questions as to how long they should wash the mouthpiece for, and what temperature of water. It's unclear that subjects would have articulated this knowledge on their own without prompting. I believe that a more effective study design would have been to have a sink available in the room that they were not "led to" but rather that they could have used if they chose to perform the washing step.

Also of note, although the correct label comprehension response for initial priming was spraying "four times", in the behavioral study spraying just one time considered correct.

Sponsor Reported Results

The percentage of participants who successfully demonstrated each direction in the package insert was calculated. The Sponsor stated that the aim of the analysis was to identify performance of each item and not a cumulative score.

Table 13: Sponsor Reported Results of Behavioral Study - % Correct, N=61

Step	Changed from old formulation?	Safety Risk	Rationale	Objective	Performance
Priming					
Remove the cap	Y	None		For information only	93.4%
Shake the inhaler	Y	Significant	Shaking ensures that the medication is evenly mixed and distributed. If not performed, it could create uneven distribution of the	Primary	73.8%

			medication and ingredients. For dosing immediately after the priming, the first actuation has the potential to provide an uneven amount of medication and not provide immediate relief.		
Hold inhaler with dose indicator up	Y	Significant	If the dose indicator is not in the "up" position during the actuation of the inhaler, it could cause the propellant only to be discharged. If this process continued over the life of the product, the propellant would be completely discharged and the inhaler would fail to provide any medication.	Primary	93.4%

Spray into the air at least one time	Y	Significant	If the inhaler is not sprayed during the priming process, priming would not be achieved. As a result, the first dose of medication the user received has the potential to be less than adequate.	Primary	82%
Cleaning					
Remove the cap	N	None		For information only	100%
Remove the container	N	Significant	If the canister is not removed during the cleaning process, the actuator opening could not be confirmed to be cleaned as an adequate amount of water would not be passed through any hole. This could lead to a clogging of the actuator and a failure of medication	Primary	93.4%

			to be received during the dosing process.		
Wash the mouthpiece through the opening	Y	Significant	If water is not passed through the opening during the washing process, the spray hold could become clogged.	Primary	77%
Wash the mouthpiece through the opening for 30 seconds	Y	Significant	If the opening is not washed for 30 seconds during the washing process, the spray hole could become clogged.	Primary	93%
Wash mouthpiece through top	Y	Significant	If water is not passed through the top during the washing process, the spray hole could become clogged.	Primary	63.9%
Mention warm water should be used	N	Significant	N/A	Primary	96.7%
Shake off excess water	Y	Low	If excessive water is not removed from the	For information only	77%

			inhaler and the inhaler is not allowed to dry overnight or by repriming, the first spray of the inhaler could be disrupted as it would still have water in the spray hold. During subsequent sprays, the water would be removed and the inhaler would function properly.		
Dry completely (either overnight or reprime)	Y	Low	If the inhaler was not allowed to dry completely, the labeling instructs the user to re-prime inhaler.	For information only	95.1%
Reassemble	Y	None	N/A	For information only	63.9%
Reassemble					
Attach removable cap to mouthpiece	Y	Significant	N/A	Primary	88.5%
Insert container in mouthpiece	Y	None	N/A	For information only	98.4%

Finger Placement					
Place forefinger in the center of the dose indicator	Y	Significant	If the user does not place finger on the center of the dose indicator, it could cause the canister to be tilted to the side and cause a release of additional medication through the valve stem. This could cause less medication in the canister than accounted for on the dose indicator. The user could continue to use the inhaler as the dose indicator would show actuations left.	Primary	88.5%
Dosing					
Take cap off mouthpiece	N	Low		For information only	98.4%
Shake inhaler before inhalation	Y	Significant	Failure to shake has the potential to provide an uneven	Primary	75.4%

			amount of medication to the user and not provide immediate relief for the asthma symptoms.		
Place thumb on bottom and finger on top of container	N	Low		For information only	100%
Empty the lungs by exhaling	N	Moderate	Failure to exhale or partially exhaling prior to the dosing process will not allow the user to inhale the medication	Secondary	85.2%
Place mouthpiece in mouth	N	Moderate	Not placing the mouthpiece into the mouth will result in the user not getting medication into the mouth/lungs	Secondary	100%
Lips closed around the mouthpiece	N	Moderate	If the user fails to close their lips around the mouthpiece, there will be the possibility that some medication	Secondary	98.4%

			will escape through the opening. This could result in a partial dose getting to the lungs. The consequence will be that the user may not get complete relief from their asthma symptoms		
Inhale	N	Significant	If the user fails to inhale, this will not allow for the medication to get into the lungs.	Primary	100%
..while squeezing the mouthpiece and container together	N	Significant	If the user fails to squeeze the mouthpiece together there are two possible concerns. The first is completely failing to depress it and therefore not providing an actuation. If this happens, the user will not get any medication. The second possibility is	Primary	98.4%

			that the user will not perform the sequence of the actuation of starting the inhalation and then actuating when continuing the breath. If this occurs the user might not get a complete dose of medication		
..pressing on the center of the dose indicator	Y	Significant	If the user does not place a finger on the center of the dose indicator, it could cause the canister to be tilted to the side and cause a release of additional medication through the valve stem. This could cause less medication in the canister than accounted for on the dose indicator. The user	Primary	98.4%

			would continue to use the inhaler as the dose indicator would show actuations left.		
Continue the deep breath	N	Moderate	If the user fails to continue their breath, the user might not get a complete dose of medication. The consequence will be that the user may not get complete relief from their asthma symptoms.	Secondary	98.4%
Hold breath	N	Moderate	If the user fails to hold their breath, the user might not get a complete dose of medication. The consequence will be that the user may not get complete relief.	Secondary	93.4%
Release (by releasing forefinger from the	N	None		For information only	100%

container					
Remove inhaler from mouth	N	None		For information only	100%
Exhale slowly	N	Moderate	If the user fails to exhale slowly, the user might not get a complete dose of medication.	Secondary	90.2%
Keep lips nearly closed	N	Moderate	If the user fails to keep their lips nearly closed, the user may not get a complete dose of medication.	Secondary	96.7%
Replace cap	N	None		For information only	82%

Of note, although "pressing on the center of the dose indicator" is a significant step (which the Sponsor asserts that most subjects appeared to have performed correctly), the labeled directions do not actually instruct users to do this; instead the wording is "*place finger on the center of the dose indicator.*" Placing and pressing are two different steps. From a review of the videotapes, it's extremely hard to tell which of the two actions occurred. In fact, most of the inhalation actions –as they were performed very quickly – were very difficult to parse out – from the videotapes at least – whether they were performed correctly. It's possible that only an actual use study, in which subjects were dosing with actual product during an asthma episode, would provide sufficient insights into whether they were able to correctly take an inhalation according to the labeled instructions.

Another issue has to do with reassembling the inhaler. In the behavioral study, reassembling was considered correct if the pieces were fit back together quickly. However, it is possible that they may not have been put back together totally correctly. Since there wasn't placebo spray in the product and a subsequent spray was not assessed, it was impossible to test whether this had occurred.

In addition to analyzing how many subjects performed each of numerous tasks correctly (including some tasks that were either self-evident or not as essential as others), we did an analysis of how many subjects performed all necessary steps in each task correctly:

Table 14: Percentage of Subjects Who Performed all Necessary Steps in Each Task Correctly

	Performance Rate % Correct (n/N)	95% CI *
Priming+	**57.4% (35/61)**	**(44.1, 70.0)**
Shake inhaler	73.8% (45/61)	(60.9, 84.2)
Hold inhaler with dose indicator up	93.4% (57/61)	(84.1, 98.2)
Spray into air at least one time	82.0% (50/61)	(70, 90.6)
Cleaning+	**50.8% (31/61)**	**(37.7, 63.9)**
Remove container	93.4% (57/61)	(84.1, 98.2)
Wash mouthpiece through opening	77.0% (47/61)	(64.5, 86.9)
For 30 seconds^	72.1% (44/61)	(59.2, 82.8)
Wash mouthpiece through the top	63.9% (39/61)	(50.6, 75.8)
Wash mouthpiece with warm water	96.7% (59/61)	(88.7, 99.6)
Finger Placement+	**88.5 (54/61)**	**(77.8, 95.3)**
Place forefinger in the center of the dose indicator	88.5 (54/61)	(77.8, 95.3)
Medicating+	**73.8 (45/61)**	**(60.9, 84.2)**
Shake inhaler before inhalation	75.4% (46/61)	(62.7, 85.5)
Empty the lungs by exhaling	85.2% (52/61)	(73.8, 93)
Place mouthpiece in mouth	100% (61/61)	(94.1, 100.0)
Lips closed around the mouthpiece	98.4% (60/61)	(91.2, 100)
Inhale	100% (61/61)	(94.1, 100.0)
While squeezing mouthpiece and container together	98.4% (60/61)	(91.2, 100)
Pressing on center of dose indicator	98.4% (60/61)	(91.2, 100)
Continue the deep breath	98.4% (60/61)	(91.2, 100)
Hold breath	93.4% (57/61)	(84.1, 98.2)
Exhale slowly	90.2% (55/61)	(79.8, 96.3)
Keep lips nearly closed	96.7% (59/61)	(88.7, 99.6)

Source: Behavioral Stats

*** 2-sided 95% exact confidence interval**
+ Required subject to complete all subtasks correctly for a particular task, e.g. Medicating, to be considered correct
^ In the study report, the Applicant computed percentages based on only the #subjects who washed the mouthpiece through the opening (n=47). I have provided percentages based on the total number of subjects

As detailed in the table, subjects had significant difficulties completing all of the key priming and cleaning steps and as discussed above, it is hard to ascertain from this methodology the extent to which they would be able to perform all of the necessary key steps in administering a correct inhalation.

The Sponsor acknowledges that there were problem areas particularly with respect to shaking the device prior to priming or dosing and cleaning the mouthpiece by washing through the opening and the top for 30 seconds each. The Sponsor asserts that while participants underperformed in these areas, these are both areas that would be expected to improve with continued use and familiarity with the product. I don't see how that can be assumed to be the case; that may be an area ripe for exploration with an actual use study.

The Sponsor further asserts in S0022 (2/21/2014) that they conducted a root cause investigation of specific steps being "off goal" and concludes that it "was likely due to the fact that part of the Primatene Mist CFD previous users who were included in the study were too dependent on their prior experiences of using Primatene Mist CFC, and did not pay close attention to the changed new instructions during the behavioral study." The Sponsor goes on to hypothesize that should the Primatene Mist CFC users realize the difference between Primatene Mist CFC and E004 for care and use, the identified root cause would have no impact on device performance and would not result in potential issues for efficacy or safety.

Table 15 Study Results for Primatene Mist CFC User and Non-User Subgroups (% Correct)

#	"Off-Goal" Step"	Total (n=61)	Primatene Mist CFC Previous User	Non Previous User	Difference of Percentage of the Two Subgroups
1	"Shake the inhaler" prior to priming	45 (74%)	6 (75%)	39 (74%)	-1%
2	"Shake the inhaler before inhalation"	48 (75%)	6(75%)	40 (76%)	1%

3	"Priming prior to use ("Spray at least 1 time into the air)	50 (82%)	5 (62.5%)	45 (85%)	22.5%
4	"Wash the mouthpiece through the top"	39 (64%)	3 (38%)	36 (68%)	30%
5	"Wash the mouthpiece through the opening	47 (77%)	5 (63%)	42 (79%)	16%

Although it's possible that former Primatene users may be significantly contributing to the problem, there weren't enough former Primatene users (n=8) in this study with which to definitively draw such a conclusion. Moreover, if this is the case, the former users will need to "realize" that the product is different not by trial and error – through which they may underdose – but rather through a label that more clearly delineates how this product is different from the previous formulation of Primatene.

Finally, I analyzed 20 of the 61 videotapes. (The 20 subjects were mostly chosen from a list that the Sponsor provided in IR #16 of the instances in which interviewers disagreed on how subjects performed certain tasks). In doing so, I discovered some additional limitations of this study:

- In the priming action, three subjects out of 20 (# (b) (6)) shook the inhaler and then sprayed it into their mouth, rather than into the air. The study did not provide totals of how many of the 61 subjects did this.

- Two subjects (# (b) (6) primed the inhaler by holding it sideways. The study did not provide totals of how ma the 61 subjects did this.

- Although failure to remove the container when washing was assessed in the study, difficulty in removing the container was not. There were five subjects out of the 20 (b) (6)) who knew that they should remove the canister to wash the inhaler but had a good deal of difficulty in doing so. For the most part, they attempted to pull it out by twisting the top rather than by pulling it out I wonder if in real life these people would either forgo washing or wash with the

  container in the inhaler (as one other subject - # (b) (6) appeared to do). The study did not provide totals of how many of the 61 subjects did this.

- In one instance the interviewer directed the subject to "turn the page" (# (b) (6) to find the instructions associated with a particular task. Interviewers were not supp d to prompt subjects with respect to locating answers.

4. Additional Perspectives on LCS 1, 2, 3 and Behavioral Study

1. First, with respect to FDA concerns that were articulated during development phase, neither the LCS studies nor the behavioral study (which follows this discussion) actually assessed whether consumers would know that the inhaler needed to be primed before first use, and whether they would know that the inhaler had to be cleaned:

    - The LCS contained no primary communications objective on priming before first use. Instead, the objective on the need to prime before first use was an "informational objective" and the relevant question was very directed:

      Q4 (LCS 2): According to the package insert, how many times do you need to prime the inhaler before you use it for the first time?

      This was not an open ended question to assess whether consumers understood about the need to prime. Instead, the question informed respondents about the need to prime and instead only asked about the *number* of times that they needed to perform this task.

    - In contrast, regarding the need to reprime when not having used in two days and/or when wet, the Sponsor did ask an open ended question:

      Q2 (LCS 3): John cleaned his inhaler and it was still wet. Now he must use it before it is dry. What does the insert say he should do?

    - A similar issue arises in the LCS with regard to the necessity of cleaning the inhaler, which was a secondary communications objective:

      Q3 (LCS 3): According to the package insert, how often should the mouthpiece be cleaned?

      Again, this was not an open ended question designed to assess whether consumers understood about the need to clean. Instead, the question informed respondents about the need to clean and instead only asked about *how often* this should be done.

    - The behavioral study (which follows this discussion) had similar directed questions. Related to priming and cleaning, they were:

      "*Show me how you would prime the inhaler."*

"Show me how you would clean the inhaler"

A far better way to have discerned whether subjects in the behavioral study knew what they were supposed to do would have been to ask them to simulate use of the product from the moment they first took it out of the package to the end of the first day they were using it. This would have compelled the subjects to walk through whatever they procedures needed to be done, without being cued as to what they were.

2. Second, the LCS studies and behavioral studies differ greatly with respect to the Sponsor's assessment of risk involved if users do not comprehend certain aspects of the directions with respect to how they use the product. This assessment of risk informed the thresholds. Typically, primary objectives with significant risks are assessed at thresholds of 90% or higher, rather than 85%. These contradictions make it difficult to fully assess the implications of the label comprehension and behavioral scores within the context of the said thresholds.

Table 11: Differences between LCS and Behavioral Study Risk Assessments for Similar Objectives

Objective	LCS Risk	LCS Rationale	Behavioral Risk	Behavioral Rationale
The inhaler should be cleaned at the end of the day after use.	Low	The previous Primatene Mist product already included the requirement for cleaning. However, it provided cleaning to be performed after each use. With the same cleaning step, the updated label requires cleaning the unit after each day of use (as opposed to each use) which is less stringent and reduces the	Significant	If the container is not removed during the cleaning process, the actuator opening could not be confirmed to be cleaned as an adequate amount of water water would not be passed through the spray hole. This could lead to a clogging of the actuator and a failure of

		clinical risk since consumers have been in the practice of more frequent cleaning. In addition cleaning is a requirement for all MDI products and therefore the risk threshold is further reduced.		medication to be received during the dosing process.
You must maintain (reprime) your inhaler under specific circumstances	Low	With regard to priming and repriming of the unit, since the subsequent sprays would provide relief and given that the actual behavior studies were designed to confirm compliance, it was determined that this clinical risk was adequately mitigated.	Significant	During the priming process, shaking of the inhaler ensures that the medication is evenly mixed and distributed throughout the canister. This is achieved through shaking during the priming process. If shaking is not performed, it could create uneven distribution of the medication and ingredients during subsequent actuation. For dosing immediately after the priming, the

				first actuation has the potential to provide an uneven amount of medication to the user and not provide immediate relief to the asthma symptoms. If the inhaler is not sprayed during the priming process, priming would not be achieved. As a result, the first dose of medication the user received has the potential to be less than adequate.

3. Third, in both the first Label Comprehension Study (LCS 1) and in the behavioral study, there were suboptimal cohorts of former Primatene users. In LCS 1, 310 respondents had missing data for this particular data field. In the behavioral study, only 8/61 (13%) of subjects were former Primatene users. Although this approximates the LCS 3 cohort with respect to overall percentage, the qualitative nature of the behavioral study necessitated, I believe, a larger cohort of former Primatene users so as to make more valid inferences. As Section 2 above outlined, FDA stated that studies needed to include a cohort of former Primatene users so as to be able to fully assess whether previous use potentially contributed to misconceptions as to how to use the product.

Table 12 : Have you used Primatene Mist within the past five years?

	LCS 1	LCS 2	LCS 3	Behavioral Study
Yes	71 (16.4%)	100 (22.6%)	62 (13.2%)	8 (13%)
No	51 (11.8%)	342 (77.4%)	406 (86.2%)	53 (87%)
Missing	310 (71.8%)		3 (0.6%)	
Total	432	442	471	61

4. Fourth, across the four studies there were minimal efforts to ensure that low literacy respondents were assessed against target thresholds. In the three label comprehension studies, although the total proportion of low literates in the sample was 25% (a reasonable percentage), the target thresholds were only assessed against the normal literates and not a general population sample that comprised of both normal literates and some percentage of the low literates. Although FDA's *Guidance for Industry: Label Comprehension Studies for Nonprescription Products* does not explicitly state that low literates need to be in the cohorts assessed against the a priori thresholds, it is an implicit assumption and one that is almost always followed by Sponsors in conducting their consumer studies. For instance, page 5 states that:

   "To adequately test the label, the low literate subjects should consist of an equal distribution of consumers who have 4th to 8th grade reading skills or marginal functional health literacy skills."

   The lack of adequate low literacy representation in the studies is underscored by the fact that FDA told the Sponsor, after seeing a previous draft of an LCS protocol, that low literacy respondents needed to be included in the research. (Section 2)

   It is true that overall, since the LCS studies did include a nice representation of low literates, it might be possible to make broad inferences about how low, literates would interpret the label. However, I believe that the assessment against threshold should have been in a general population, comprised of both normal and low literates. Particularly in the case of this product, the Sponsor has asserted that it would provide access for populations who otherwise would not be as fully engaged with the medical system in treating their asthma as other populations. Therefore a more diverse population should have been assessed against threshold.

   Likewise, the behavioral study also had only five low literates out of a total of 61 subjects (8%). Again, since this was more of a qualitative study than the LCS studies, there should have been a larger cohort of low literates so as to be able to make more valid inferences about how they would be able to use the product.

5. Recommendations

1) Labeling should be further revised to optimize comprehension of:
    a. Not relying on the dose indicator if dropped
    b. the need to prime when first using the product
    c. the need to clean the product daily after use
    d. and the need to reprime when wet

2) Labeling should also be revised to clarify:
    a. exactly how the canister is to be removed for cleaning
    b. pressing on the center of the dose indicator is required when dosing

3) Graphics should be revised to call attention to the fact that there are new instructions for use for this formulation of Primatene.

4) A new behavioral study should be conducted with a significant cohort of former Primatene users, as well as a significant cohort of low literates.

    a. The study should not call for specific tasks to be completed; rather, it should ask subjects to emulate and demonstrate taking out the product from the package for the first time and using it at the end of the day before bedtime.

    b. The study (and videotapes) should begin from the moment the subject sits down to look at the label and insert for the first time.

    c. A sink should be provided so that full assessment of washing can be made – length of time to wash, warm water, etc, without prompting from the interviewer.

    d. The product should contain placebo spray so that a full assessment of spraying can be made, both as part of priming, as well as whether the product is still functional after the user reassembles after cleaning.

    e. Both the study report and raw data should include the number of sprays utilized in priming for the first time. The study report did not specify how many subjects sprayed four times and how many sprayed just once (which was considered correct)

    f. Both the study report and raw data should document how many user errors were seen for 1) difficulty in getting the canister out of the inhaler for cleaning 2) how many subjects sprayed into their mouth for priming instead of the air 3) how many subjects primed the pump horizontally instead of vertically

    g. Dose undercounting was not really assessed as a primary objective in the label comprehension study (other than that related to dropping, in which the

comprehension was not high). Additional user research related to comprehension of the implications of dose undercounting is recommended. Possibly it can be incorporated into the behavioral study in the form of a question at the end (ie, the product was inhaled and sprayed a number of times – why hasn't the dose indicator reflected a decrease in the number of available doses)

5) A scaled down actual use study may be of use to fully assess how users would be able to dose with and manage the new inhaler product.

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1. According to the package insert, when should the mouthpiece be cleaned?

Do not read answer alternatives

Check all that apply

- ☐ At the end of the day (after use)
- ☐ After use / after each use
- ☐ Other
- ☐ Don't Know

Correct: Box 1 or 2 is checked

2. After cleaning, if the inhaler must be used before the mouthpiece is dry, what should you do before you can use it?

Do not read answer alternatives
Check all that apply

- ☐ Reprime one time
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked

3. How do you tell how many sprays you have left in the inhaler?

Do not read answer alternatives
Check all that apply

- ☐ (Look on) the dose indicator
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked

4. About how many sprays are there in a full inhaler?

Do not read answer alternatives
Check all that apply

- ☐ About 160 (more than/ beyond 160)
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked

5. What does the dose indicator do?

Do not read answer alternatives
Check all that apply

- ☐ Shows the number of remaining sprays/counts down the number of sprays
- ☐ Counts down 20's/20
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked
Acceptable: Box 2 is checked

6. According to the package insert, what does it mean when the red zone appears on the dose indicator?

- ☐ you should obtain a new inhaler soon / replace your inhaler
- ☐ You are almost out of medicine

☐ Other
☐ Don't Know

Correct: Box 1 is checked
Acceptable: Box 2 is checked

Some of these next questions will be made-up examples of people who might want to use or who are using Primatene; I will ask you what the label says they should or shouldn't do.

7. **Sally has not used her inhaler for a week. What, if anything, does she need to do to it before using it again?**

Do not read answer alternatives
Check all that apply

☐ Reprime / Maintain
☐ Shake it
☐ Spray once into the air
☐ Nothing
☐ Other
☐ Don't Know

Correct: Box 1 checked or (Box 2 and 3 checked)

8. **Jessica has just started using this inhaler for the first time. She has used two inhalations but noticed that the dose indicator hasn't changed. What does the package insert say about this?**

Do not read answer alternatives
Check all that apply

☐ The counter counts down by twenty (after 20 sprays)
☐ Other
☐ Don't Know

Correct: Box 1 is checked

9. **Robert uses Primatene several times a week and usually carries it around with him. This morning he dropped his inhaler in the parking lot, so he reprimed it. Is there anything else that the package insert says Robert should do?**

Do not read answer alternatives
Check all that apply

☐ Do not rely on the dose indicator
☐ Keep track of the number of sprays you use on your own records
☐ Reprime
☐ Other
☐ Don't Know

If box 1 checked but not box 2, ask:

9a. If Robert can't rely on the dose indicator, what, if anything does the package insert say Robert should do?

Do not read answer alternatives

Check all that apply

- ☐ Keep track of the number of sprays you use on your own records
- ☐ Other
- ☐ Don't Know

Correct: (Box 1 and Box 2 is checked in Q14) or (Box 1 in Q14 and Box 1 in 14a)
Acceptable: Box 1 or Box 2 is checked is checked in Q14 or Box 1 checked in Q14a

10. After using the inhaler, Jen noticed that the dose indicator was zero, but when she shakes the device she can tell there is medicine left in it. What does the package insert say about this?

Do not read answer alternatives

Check all that apply

- ☐ The dose indicator will stop counting at "0"
- ☐ Inhaler must be replaced
- ☐ Even though there may be medication in the container when the dose indicator hits zero,
- ☐ The correct dose cannot be assured.
- ☐ Do not rely on the dose indicator
- ☐ Keep track of the number of the number of sprays you use on your own records
- ☐ Never try to change the numbers
- ☐ Never try to take the dose indicator off the metal canister
- ☐ The dose indicator cannot be reset
- ☐ Other
- ☐ Don't Know

Correct: Box 2 OR Box 4 checked

11. Jean sees that the dose indicator reads zero but she knows there is more medicine in the inhaler so she decides to change the dose indicator to show more sprays. What does the package insert say about this?

Do not read answer alternatives

Check all that apply

- ☐ Never try to change the numbers
- ☐ The dose indicators cannot be reset
- ☐ Never try to take the dose indicator off the metal canister
- ☐ It should remain permanently attached to the container

☐ The correct dose in each spray cannot be assured
☐ Other
☐ Don't Know

Correct: Box 1 or Box 2 is checked

DRUG FACTS LABEL QUESTIONS

Take back the package insert and hand the participant the Drug Facts label information.

Here is some additional information about the same product. Please take whatever time you need to read this carefully.

I will be asking you some questions about what you read. As before, this is not a test of your memory, so please feel free to re-read the information. Also, it is very important to base your answers on what you read on the label, not on your own experience or opinions.

12. What is this product used for?

Do not read answer alternatives
Check all that apply

☐ mild
☐ symptoms
☐ intermittent
☐ asthma
☐ wheezing
☐ tightness of chest
☐ shortness of breath
☐ Don't Know

If only Box 4 is checked:

12a. What type of asthma does it treat?

☐ mild
☐ symptoms
☐ intermittent

Correct: (Box 1 or Box 3) and Box 4 are checked in Q1
Acceptable: Box 4 checked in Q1 and Box 1 or 3 checked in Q1a

13. There are several warnings under the Asthma Alert. If any of these conditions happen, what might this be a sign of?

Do not read answer alternatives
Check all that apply

☐ Your asthma may be getting worse
☐ See a doctor

- ☐ may be life threatening
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked

14. According to the 'When using this product' section of the label, what are some of the risks associated with this product?

Do not read answer alternatives
Check all that apply

- ☐ blood pressure may go up
- ☐ heart rate may go up
- ☐ Increased risk of heart attack
- ☐ Increased risk of stroke
- ☐ Death
- ☐ Asthma getting worse
- ☐ Difficulty sleeping
- ☐ Tremors, nervousness or seizures
- ☐ Don't Know
- ☐ Other

Correct: Any two of Box 1, Box 2, Box 3, Box 4, are checked
Acceptable: Box 1, Box 2, Box 3, or Box 4 is checked

15. According to the label, what are the things that may increase the risk of heart attack or stroke when using this product?

Do not read answer alternatives
Check all that apply

- ☐ A history of high blood pressure
- ☐ A history of heart disease
- ☐ Taking this product more often (than directed)
- ☐ Taking more than the recommended dose
- ☐ using caffeine
- ☐ using stimulants
- ☐ Other
- ☐ Don't Know

Correct: Any two of Box 1, Box 2, Box 3, Box 4, are checked
Acceptable: Box 1, Box 2, Box 3, or Box 4 is checked

Some of these next questions will be made-up examples of people who might want to use or who are using Primatene; Again, I will ask you what the label says they should or shouldn't do.

16. Camille has had 4 asthma attacks in one week. According to the label, what should Camille do?

Do not read answer alternatives
Check all that apply

- ☐ See/contact her doctor
- ☐ Do not use
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked

17. Jay has been using this product for his asthma. Sometimes he notices that his heart beats faster than usual. According to the label, what should Jay do?

Do not read answer alternatives
Check all that apply

- ☐ Stop use
- ☐ Ask a doctor
- ☐ Avoid caffeine or stimulants
- ☐ Other
- ☐ Don't Know

Correct: Box 1 and Box 2 are checked
Acceptable: Box 1 or Box 2 is checked

18. Jayne has been using Primatene to treat her asthma symptoms for a few months. She has noticed recently that she has difficulty sleeping. What does the label say Jayne should do?

Do not read answer alternatives
Check all that apply

- ☐ Stop use
- ☐ Ask a doctor
- ☐ Other
- ☐ Don't Know

Correct: Box 1 and Box 2 are checked
Acceptable: Box 1 or Box 2 is checked

19. For adults and children 4 years of age and older, according to the label how many inhalations is in a dose?

Do not read answer alternatives
Check all that apply

- ☐ 1 to 2
- ☐ 1
- ☐ 2
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked
Acceptable: Box 2 or 3 is checked

20. Charlotte took one inhalation and waited for a minute; her asthma symptoms were not relieved so she took another inhalation. How long should she wait to use Primatene again?

Do not read answer alternatives
Check all that apply

- ☐ (At least) 4 hours
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked

21. According to the label, what is the maximum number of inhalations a person should use in a 24 hour period?

Do not read answer alternatives
Check all that apply

- ☐ 8
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked

22. Megan has a 3 year old son who has asthma. What instructions does the label give Megan about giving this medicine to her son?

Do not read answer alternatives
Check all that apply

- ☐ Ask a doctor
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked

Appendix 5: Case Report Form for LCS 2

1. **According to the package insert, how many times do you need to prime the inhaler before you use it for the first time?**
   Do not read answer alternatives
   Check all that apply
   - ☐ 4 times
   - ☐ Other
   - ☐ Don't Know

   Correct: Box 1 is checked

2. **According to the package insert, how often should the mouthpiece be cleaned?**
   Do not read answer alternatives
   Check all that apply
   - ☐ Daily
   - ☐ After use / after each use
   - ☐ After it has been dropped
   - ☐ if it becomes dirty
   - ☐ Other

☐ Don't Know

Correct: Box 1 is checked

Some of these next questions will be made-up examples of people who might want to use or who are using Primatene; I will ask you what the label says they should or shouldn't do.

3. **John cleaned his inhaler and it is still wet. Now he must use it *before* it is dry. What does the insert say he should do?**

Do not read answer alternatives
Check all that apply

- ☐ Reprime one time
- ☐ Let it dry overnight/Air dry
- ☐ Other
- ☐ Dry it off / wipe it off
- ☐ Nothing
- ☐ Don't Know

If Box 2 is checked, but not 1, ask:

3a. If John cannot let it <dry overnight or air dry>, and still must use it before it is dry, what does the package insert say John should do?

Do not read answer alternatives
Check all that apply

- ☐ Reprime one time
- ☐ Dry it off / wipe it off
- ☐ Other
- ☐ Don't Know

Correct: (Box 1 is checked in Q3) or (Box 2 in Q3 and Box 1 in 3a)

4. **How do you tell if you have any sprays left in the container?**

Do not read answer alternatives
Check all that apply

- ☐ (Look on) the dose indicator
- ☐ Look for the red zone/ if the red zone is not visible
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked
Acceptable: Box 2 is checked

5. **About how many sprays are there in a full container?**

Do not read answer alternatives

Check all that apply

- ☐ 160 (about160)
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked

6. **What does the dose indicator do?**

Do not read answer alternatives
Check all that apply

- ☐ Shows the number of remaining sprays/counts down the number of sprays
- ☐ Lets you know when to replace your inhaler
- ☐ Counts down by 20's/20
- ☐ Other
- ☐ Don't Know

Correct: Box 1 or Box 2 is checked
Acceptable: Box 3 is checked

7. **According to the package insert, what does it mean when the red zone appears on the dose indicator?**

- ☐ You should buy a new inhaler soon / replace your inhaler
- ☐ You are almost out of medicine
- ☐ There are 20 sprays left
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked
Acceptable: Box 2 or Box 3 is checked

8. **Sally has not used her inhaler for about a week. What, if anything, does she need to do to the inhaler before using it again?**

Do not read answer alternatives
Check all that apply

- ☐ Reprime
- ☐ Shake it
- ☐ Spray
- ☐ Clean it
- ☐ Nothing
- ☐ Other
- ☐ Don't Know

If Box 4 checked but not Box 1, or Box 2 and Box 3, ask:

8a. After Sally has cleaned the inhaler, is there anything, else should she do?

Do not read answer alternatives

Check all that apply

- ☐ Reprime
- ☐ Shake it
- ☐ Spray
- ☐ Nothing
- ☐ Other
- ☐ Don't Know

Correct: Box 1 or (Box 2 AND Box 3) is checked in Q8 OR (Box 4 in Q8 and Box 1 in Q8a) OR (Box 4 in Q8 and Box 2 and Box 3 in 8a)

9. How many sprays does it take for the dose indicator number to change?

Do not read answer alternatives

Check all that apply

- ☐ The counter counts down by twenty /After 20 sprays
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked

10. Robert dropped his inhaler so he cleaned and reprimed it. Is there anything else that the package insert says Robert should do as he uses his inhaler again?

Do not read answer alternatives

Check all that apply

- ☐ Do not rely on the dose indicator
- ☐ Keep track of the number of sprays you take
- ☐ Clean it
- ☐ Reprime
- ☐ Other
- ☐ Don't Know

Correct: Box 1 and Box 2
Acceptable: Box 1 or Box 2

11. After using the inhaler, Jen noticed that the dose indicator was in the red zone and was showing zero, but when she shakes the inhaler it sounds like there is medicine left in it. What does the package insert say about this?

Do not read answer alternatives

Check all that apply

- ☐ The dose indicator will stop counting at "0"
- ☐ Inhaler must be replaced/stop using/throw away
- ☐ The correct dose cannot be assured.
- ☐ Do not rely on the dose indicator
- ☐ Never try to change the numbers
- ☐ Never try to take the dose indicator off the container
- ☐ Other
- ☐ Don't Know

Correct: Box 2 OR Box 3 checked
Acceptable: Box 1 checked

12. Jean decides to change the dose indicator to show more sprays. It did not work so she tried to remove the dose indicator. What does the package insert say about this?

Do not read answer alternatives
Check all that apply

- ☐ Never try to change the numbers
- ☐ The dose indicators cannot be reset
- ☐ Never try to take the dose indicator off the container
- ☐ It should remain permanently attached to the container
- ☐ The correct dose in each spray cannot be assured
- ☐ Other
- ☐ Don't Know

Correct: Box 1 and Box 3 checked
Acceptable: Box 1 or Box 2 or Box 3 or Box 4 is checked

Appendix 6: Case Report Form for LCS 3

1. **According to the package insert, how many times do you need to prime the inhaler before you use it for the first time?**

Do not read answer alternatives

Check all that apply

- ☐ 4 times
- ☐ Other
- ☐ Don't Know

Correct: Box 1 is checked

Some of these next questions will be made-up examples of people who might want to use or who are using Primatene; I will ask you what the label says they should or shouldn't do.

2. **John cleaned his inhaler and it is still wet. Now he must use it *before* it is dry. What does the insert say he should do?**

Do not read answer alternatives

Check all that apply

- ☐ Prime
- ☐ Prime one time
- ☐ Shake
- ☐ Spray
- ☐ Let it dry overnight/Air dry
- ☐ Dry it off / wipe it off
- ☐ Other
- ☐ Nothing
- ☐ Don't Know

If only Box 5 or Box 6 is checked, ask:

2a. If John cannot let it <dry overnight or air dry>, and still must use it before it is dry, what does the package insert say John should do?

Do not read answer alternatives

Check all that apply

- ☐ Prime
- ☐ Prime one time
- ☐ Shake
- ☐ Spray
- ☐ Dry it off / wipe it off
- ☐ Other
- ☐ Don't Know

Correct: (Box 1 or Box 2 is checked in Q2) or (Box 3 and 4 in Q2) or ((Box 5 or 6) in Q2 and (Box 1 or Box 2 in Q2a)) or ((Box 5 or 6) in Q2 and (Box 3 and 4 in Q2a))

3. **Sally has not used her inhaler for more than two days. What does she need to do to the inhaler before using it again?**

Do not read answer alternatives

Check all that apply

- ☐ Prime
- ☐ Prime one time
- ☐ Shake it

- ☐ Spray
- ☐ Clean it
- ☐ Nothing
- ☐ Other
- ☐ Don't Know

If only Box 5 is checked ask:

3a. After Sally has cleaned the inhaler, is there anything else she should do?

Do not read answer alternatives

Check all that apply

- ☐ Prime
- ☐ Prime one time
- ☐ Shake it
- ☐ Spray
- ☐ Nothing
- ☐ Other
- ☐ Don't Know

Correct: (Box 1 or Box 2) OR (Box 3 AND Box 4) is checked in Q3 OR (Box 5 in Q3 and Box 1 or Box 2 in Q3a) OR (Box 5 in Q3 and Box 3 and Box 4 in 3a)

4. What does the package insert say about the dose indicator if the inhaler is dropped?

Do not read answer alternatives

Check all that apply

- ☐ Do not rely on the dose indicator
- ☐ Keep track of the number of sprays you take
- ☐ Clean it
- ☐ Prime
- ☐ Other
- ☐ Don't Know

If only Box 3 is checked, ask:

4a. Is there anything else the Package Insert says if the inhaler is dropped?

Do not read answer alternatives

Check all that apply

- ☐ Do not rely on the dose indicator
- ☐ Keep track of the number of sprays you take
- ☐ Clean it
- ☐ Prime

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA R COHEN
05/05/2014

LUCIE L YANG
05/05/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: March 27, 2014

TO: Ryan Raffaelli, DNCE Medical Team Leader
Jennifer Pippins, DPARP Medical Officer
Daniel Reed, DNCE Regulatory Project Manager
Division of Nonprescription Clinical Evaluation (DNCE)

FROM: Sharon K. Gershon, Pharm. D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205920/ S001

APPLICANT: Amphastar Pharmaceuticals, Inc.

DRUG: Epinephrine HFA Metered Dose Inhaler

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: For temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older.

Protocol: Study API-E004-CL-C: A Randomized, Double- and Evaluator-Blinded, Active- and Placebo-Controlled, Three-Arm, Parallel, 12-Week Study in Adolescent and Adult Patients with Asthma

CONSULTATION REQUEST DATE: September 20, 2013

INSPECTION SUMMARY GOAL DATE: April 3, 2014

ADVISORY COMMITTEE MEETING: February 25, 2014

DIVISION ACTION GOAL DATE: May 21, 2014

PDUFA DATE: May 22, 2014

I. BACKGROUND:

Armstrong Pharmaceuticals (a wholly owned subsidiary of Amphastar Pharmaceuticals), previously marketed an Epinephrine CFC-Metered Dose Inhalation (MDI) under the trade name Primatene® Mist, which is Epinephrine Inhalation Aerosol with chlorofluorocarbons (CFCs) as propellants. Due to environmental concerns, CFCs were mandated to be replaced by non-CFC propellants by the end of 2011. The applicant Amphastar Pharmaceuticals has developed a new formulation with HFA-134a (b) (4) as propellant: Epinephrine HFA-MDI (E004). HFA-134a is considered a suitable replacement for CFC propellants because of its chemical inertness, low toxicity, and minimal ozone-depleting potential. For E004, Armstrong is proposing the same indications previously held for Primatene® Mist, updated to meet the current OTC monograph for bronchodilator drug products containing epinephrine for "the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older."

Epinephrine administered by oral inhalation is associated with a rapid and effective delivery to the respiratory tract. (b) (4) . The advantages of administering epinephrine via a metered dose inhaler (MDI) include: i) rapid onset, ii) short duration of action, (iii) low cost, (iv) over-the-counter (OTC) availability, and (v) ease of inhalation versus injection.

The present study (API-E004-CL-C) took place at 34 sites in the U.S., and was intended to evaluate the long-term efficacy and safety of Epinephrine HFA Metered Dose Inhaler (E004) in comparison with placebo control and active drug. The study was a long-term (12 week), multiple dose study performed with approximately 373 adolescent and adult subjects with documented intermittent, or mild-to-moderate asthma for at least six months, in a randomized, active- and placebo-controlled, double- or evaluator-blinded, three-arm, parallel, multi-center setting. The study used a randomized ratio of 4:1:1 for three treatment groups: E004 (Arm T), placebo-HFA (Arm P), and Primatene® Mist (Arm A). The study consisted of a screening visit and five (5) study visits. The five (5) study visits were scheduled at 3-week intervals, as Visit 1 (Day 1 of study), Visit 2 (week 3), Visit 3 (week 6), Visit 4 (week 9), and Visit 5 (week 12).

Serial forced expiratory volume in 1 second (FEV1) measurements were used for efficacy evaluation and therefore are critical for this clinical study. The bronchodilator effect of E004 and control arms was assessed by the change FEV1 at Visit 5 relative to the same day baseline FEV1 data.

Electronic diaries were used by all subjects to record daily QID use of study drugs, priming/wasting sprays, PRN usage of rescue medication, daytime asthma symptom score (DASS), nighttime awakening score (NAS), daily peak expiratory flow (PEF), daily assessment of device malfunction and cleaning.

II. RESULTS (by Site): A total of 34 U.S. sites participated in this study. The Review Division selected two sites for GCP inspections. These two sites demonstrated a larger treatment effect for study drug compared to other sites and also enrolled an average or greater than average number of patients. The Sponsor Armstrong Pharmaceuticals, Inc. is a small company and has no prior inspectional history. OSI decided to inspect the Sponsor because their first submission resulted in a Refusal to File, and was aware that the application would be of particular interest because of the use of a non-chloroflourocarbon propellant.

Name of CI/Sponsor/Address	**Protocol # and Site # and # of Subjects**	**Inspection Dates**	**Final Classification**
Craig F. LaForce, North Carolina Clinical Research 2615 Lake Drive, Suite J01 Raleigh, NC 27607	API-E004-CL-C Site #18 18 subjects	November 13 – 22, 2013	NAI
Andrew J. Pedinoff Princeton Center for Clinical Research 24 Vreeland Drive Skillman, NJ 08558	API-E004-CL-C Site #20 12 subjects	December 10-20, 2013	NAI
Amphastar Pharmaceuticals 11570 6th Street Rancho Cucamonga, CA 91730	Sponsor Inspection API0E004-CL-C	February 27 – March 3, 2014	Pending (Preliminary NAI)

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Craig F. LaForce,
North Carolina Clinical Research
2615 Lake Drive, Suite J01
Raleigh, NC 27607

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. [redacted] (b) (4). He was last inspected in September 2011 and that inspection was classified NAI. This inspection included a walk-thru of facilities, review of screening and enrollment, randomization procedures, IRB approvals, financial disclosure statements, informed consent documents, case report forms, case history files, drug accountability records, primary efficacy endpoint measurements, adverse events, protocol deviations, and site monitoring logs.

The site screened 28 subjects and randomized 18 subjects to one of three treatment arms. A total of 15 subjects completed the study. Three subjects terminated early from the study, and one subject [redacted] (b) (6) was disqualified after completion. There was one subject under the age of 18 (12 years old) who completed the study.

For the 18 subject randomized, the FDA field investigator reviewed spirometry reports for FEV1 tests, (primary efficacy endpoint), and adverse event reports. For eight subjects, she reviewed vital sign measurements, demographics, adherence to visit schedules, concomitant medications, ECG reports, laboratory results, and corroborated CRF records against electronic diary records.

b. General observations/commentary: The inspector did not observe any under-reporting of adverse events, and no discrepancies in reported FEV1 values. She observed that printouts of the electronic diary entries were included in the subject files selected for review. There was also a CD in the study file containing the electronic diary information for each subject. All information from source records was entered onto paper CRFs. There were ten protocol deviations documented during the study. The FDA field investigator reported that monitoring was conducted by Amphastar, and observed five monitoring visits between June 2, 2011 and October 25, 2011.

c. Assessment of data integrity: No significant deficiencies were observed during the inspection, and no FDA form 483 was issued. OSI considers that the study was conducted well at this site, and OSI recommends that the data are acceptable in support of the study indication.

2 **Andrew J. Pedinoff**
Princeton Center for Clinical Research
24 Vreeland Drive
Skillman, NJ 08558

a. What was inspected: [redacted] (b) (4). He was last inspected in November 2004, and that inspection was classified as NAI. For this study, the site screened fourteen subjects and enrolled twelve subjects. A total of eleven subjects completed

the study. The first subject was screened on May 26, 2011, and the last follow-up for any subject occurred on November 1, 2011.

The inspection included a walk-thru of facilities, review of the screening and enrollment procedures, financial disclosure statements, and informed consent documents for all screened subjects. The FDA field investigator reviewed source documents and case report forms (CRFs) for all randomized subjects. The source documents included the following records: information about the subject at the time of entry into the study; information about subjects throughout participation in the study, including primary efficacy measurements, results of laboratory tests, and adverse events. The review also included key personnel involved in collecting data and documentation of study drug exposure.

The FDA field investigator corroborated the data in source documents, CRFs and data listings for all enrolled subjects with respect to inclusion and exclusion criteria, vital signs, laboratory values, procedures such as electrocardiograms at Visits 1 and 5, peak expiratory flow measurements, screening baseline FEV1, air-way reversibility test, serial pulmonary function tests, concomitant medications, and adverse events.

The FDA field investigator reviewed test article control and accountability records, including dispensation to study subjects and returns. The FDA field investigator reviewed site monitoring activities and email communications between the site and the sponsor concerning data queries.

b. General observations/commentary: During her review of FEV1 measurements, the FDA field investigator identified one subject (b) (6) whose pre-dose FEV1 at Visit 5 was done twice on the same day, and again within 14 days of the previous visit. The protocol specified that if a subject failed the pre-dose measurements twice on the same day, that subject should be terminated from the study. She found that the site personnel did not always document the exact quantity of IP received from the sponsor, dispensed to subjects, and returned by the subject. These items were discussed with Dr. Pedinoff at the conclusion of the inspection. No Form FDA 483 was issued. She observed a total of seven monitoring visits to this site during the conduct of the study.

c. Assessment of data integrity: No significant observations were observed, and no FDA form 483 was issued. OSI considers that the study was conducted well at this site, and OSI recommends that the data are acceptable in support of the study indication.

3. Amphastar Pharmaceuticals, Inc.
11570 6th Street
Rancho Cucamonga, CA 91730 - 6025

a. **What was inspected:** The inspection was performed in accordance to Compliance Program 7348.810 – Sponsor, Contract Research Organizations and Monitors. The facility at Rancho Cucamonga is currently serving as the firm's Corporate Headquarters, manufacturing site, and warehousing site. Armstrong Pharmaceuticals is

a wholly owned subsidiary of Amphastar, and was acquired by Amphastar in 2003. Armstrong manufactures pharmaceutical inhalation products, and is the manufacturer of for (b) (4) for this NDA.

This inspection was conducted between February 27 and March 3, 2014 and focused on the following seven investigator sites: Site #18 (LaForce), Site #20 (Pedinoff), Site #1 (James Wolfe), Site #10 (Frank McCafferty), Site #11 (Holly Brown), Site #25 (Edward Kerwin), and Site #34 (Stephen Tilles).

During the inspection, the FDA field investigator reviewed the following: the firm's training program; signing of FDA 1572 Statement of Investigators at seven sites; protocol review and approvals (API-E004-CL-C); Informed Consent Forms; signing of Financial Disclosure Statements at seven sites; test article accountability records; site initiation visit and training procedures; site monitoring; monitoring reports at seven sites; reporting of adverse events, reporting of protocol deviations; data collection process; data verification process; and primary and secondary endpoint reporting.

b. General observations/commentary: The FDA field investigator noted the following during the inspection: the sponsor maintained adequate oversight over the clinical investigators throughout the study. No deficiencies were noted in Financial Disclosure Statements and Form 1572's for seven sites.,..

The study was conducted using only one version of the protocol which was approved by the IRB prior to start of the clinical trial. Subjects signed the Informed Consent Document (ICD) prior to screening and enrollment into the study. The Sponsor provided two days training to all investigators, and that this training along with supplies, and study drug was provided to the clinical site prior to the start of the study.

With respect to monitoring, the the Sponsor had a dedicated team of well-trained in-house monitors (CRAs) to evaluate and perform ongoing monitoring of the clinical investigators throughout the study. The monitors visited the sites throughout the study at 3 to 4 week intervals and would follow-up with the corrective actions on subsequent visits. For Site #18 (Craig LaForce) and Site #20 (Andrew Pedinoff), the monitor visited the sites four times throughout the course of the study.

There were a total of 283 ADE (Adverse Drug Events) reported to the sponsor throughout the study from all 34 sites. The majority of these ADEs were classified as mild or moderate, such as cough, tremor, insomnia, headache, back pain, chest discomfort, and nausea. There were about one dozen severe ADE incidents reported to the sponsor, including tremors, acute bronchitis, asthma exacerbation, and anxiety. The field investigator noted one Serious Adverse Event (SAE) that occurred at Site (b) (6). The subject was hospitalized on (b) (6) with bronchitis and symptoms of coughing and trouble breathing. The subject was treated with oxygen and Avelox for seven days and discharged from the hospital on (b) (6) This SAE was reported to the sponsor on (b) (6)

The FDA field investigator reviewed and verified the source data with data listings for Sites #18 and #20. He did not observe any discrepancies.

c. Assessment of data integrity: No deficiencies were observed during the inspection of the Sponsor. OSI recommends the data as acceptable in support of the claimed indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two domestic clinical investigator inspections and a Sponsor site inspection were conducted in support of NDA 205920. No regulatory violations were found during the inspections of Dr. Craig LaForce (Site #18, NC) or Dr. Andrew Pedinoff (Site #20, NJ). Both inspections were classified as NAI. No regulatory violations were found during the inspection at the sponsor site Amphastar Pharmaceuticals. OSI recommends that the data from this study may be considered reliable.

Note: The final EIR for Amphastar Pharmaceuticals, Inc. was not available at the time this clinical inspection summary was written. The observations noted are based on a preliminary EIR and email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{See appended electronic signature page}

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/s/

SHARON K GERSHON
03/28/2014

SUSAN D THOMPSON
04/02/2014

KASSA AYALEW
04/02/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
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Silver Spring, MD 20993
Telephone 301-796-2200
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MEMORANDUM TO FILE

NDA [IND] Numbers: 205,920 [74,286]

Sponsor: Armstrong Pharmaceuticals, Inc.

Drug: Epinephrine inhalation aerosol, 125 mcg

Dosage form and route of administration: Dry powder for inhalation

Intended Indications: Temporary relief of mild symptoms of intermittent asthma

The consult requested that PMHS "assess the submitted pediatric data to help determine whether the applicant's proposal to market the product for children over age 12 years is safe and appropriate" for this candidate over-the-counter drug.

As noted in the prior PMHS review (E. Durmowitz, February 2, 2012), an expert panel review previously concluded that inhaled nonselective adrenergic agents, specifically including epinephrine, are not recommended for treatment asthma symptoms in any age group (neither for acute intermittent, nor chronic use) due to the potential for excessive cardiac stimulation.[1] The prior review noted that should development proceed, the determination of the need for long-term pediatric safety data should be based on an assessment of short and long-term safety data available from adult patients including any available pharmacokinetic and pharmacodynamic data.

At the mid-cycle meeting of January 7, 2014, PMHS reviewed the prior recommendations with staff from the Divisions of Pulmonary, Allergy, and Rheumatology Products (DPARP) and Nonprescription Clinical Evaluation (DNCE).

Representatives from DPARP and DNCE inquired what labeling language might be appropriate to restrict use of the drug in children for whom safety and effectiveness data are not yet available. PMHS stated that for over-the-counter drugs, language for restricting use in a particular age group is limited to "Do Not Use in patients ages", for example, "11 years and younger".

A separate consult should be submitted to PMHS by the review divisions if labeling assistance is required.

[1] Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. 2007; weblink: https://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf; accessed March 13, 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ETHAN D HAUSMAN
03/14/2014
Brief memo to file

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 5, 2013

From: Thomas A. Marciniak, M.D.
Medical Team Leader
Division of Cardiovascular and Renal Products

Subject: Cardiac safety of epinephrine inhalation aerosol, NDA 205920

Through: Norman Stockbridge, M.D., Ph.D.
Division Director

To: Daniel Reed, Regulatory Project Manager
Division of Nonprescription Clinical Evaluation

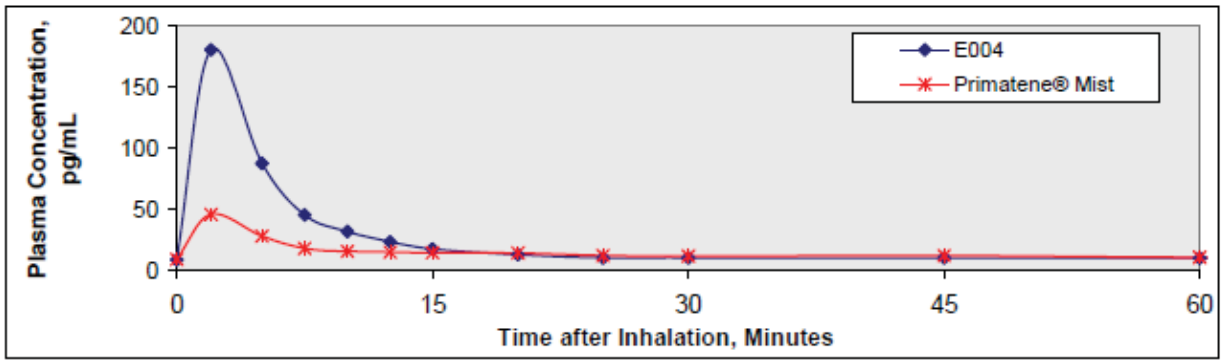
This memo is our response to your consult dated September 10, 2013, regarding the cardiac safety of epinephrine inhalation aerosol E004 with use of the drug in the OTC setting, based on the submitted analyses of the clinical trial data and postmarketing experience. You also ask us to comment on missing or incomplete data or analyses that could impact an action on this application. 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 at the proposed to-be-marketed dose.

Background

We will not repeat all the details of the history of this drug or of other inhaled bronchodilators but we will summarize the background items most relevant to cardiac safety below.

- The sponsor reformulated E004 from its predecessor Primatene Mist to replace the CFC propellant with HFA. The sponsor also changed the drug formulation from a solution to a suspension. The most pertinent result of all of the changes regarding cardiac safety is that the C_{max} of E004 (0.18 ng/mL) is 4.5 times higher than that of Primatene Mist (0.046 ng/mL.) We show the sponsor's estimates of epinephrine levels in plasma after inhalation of a normal dose of E004 and Primatene in Figure 1. The sponsor notes that the elevation is short-lived (declining 90% within 10 minutes) and less than the reported endogenous epinephrine level after moderate exercise (0.25 ng/mL for untrained subjects or 0.71 ng/mL for trained subjects with a 3 minutes running for 440 meters.) Regardless, we need to scrutinize vital sign changes around T_{max}.

Figure 1: Sponsor's Epinephrine Plasma Levels following Inhalation of E004 and of Primatene



- There is a long history of suspected safety problems with inhaled adrenergic bronchodilators. In the 1960s a dramatic increase in asthma deaths in the United Kingdom and other countries was attributed to the marketing of high strength isoproterenol (a non-selective beta agonist) inhalers that delivered a 5-fold higher dose than the usual inhalers. While epinephrine is not clearly implicated in this safety issue, the issue does illustrate that a 5-fold higher dose of an inhaled bronchodilator can produce substantially higher serious toxicity. The long acting beta$_2$ agonists (LABAs) have also shown safety issues. The SMART outcomes trial of salmeterol vs. placebo was terminated in 2002 because of slow enrollment and an increase in asthma events with salmeterol, particularly in African Americans. Several FDA advisory committee (AC) meetings (in 2005, 2007, 2008 and 2010) have addressed the SMART trial and related findings. The latest FDA action, from April 2011, was to require post-market safety trials for all LABAs.

- Conversely, the post-marketing experience with Primatene appears more benign. In a check of the AERS database for Primatene using the Empirica Signal data mining software the highest EB05 scores (ranging from 46 to 5) are for (ordered highest to lowest) respiratory tract irritation, drug abuse, pharyngitis, drug dependence, and asthma. The highest EB05 scores for cardiac AEs are for palpitation (3.1), chest pain (2.7), and heart rate increased (2.5). The highest EB05 scores for serious AEs are for loss of consciousness (1.3) and myocardial infarction (1.2). Cardiac arrest has an EBGM of 1.7 with an EB05 of 0.97. The EB05 scores for serious cardiac AEs do not reach the level that would concern us while those for the less serious AEs are ones that we might expect from a non-selective adrenergic agonist. The EB05 scores for drug abuse and drug dependence do reinforce the opinion that we need to be concerned about use of epinephrine inhalers beyond the labeled dose recommendations.

Clinical Safety Studies

We show in Table 1 a list of the clinical safety studies for E004.

Table 1: Clinical Safety Studies

Study	Design	Dosing*	E004		Control	Duration
			dose (mcg)	n		
A	Crossover single dose-ranging in asthmatics	2i	250, 320, 440	26	placebo, Primatene	(single doses)
A2	Crossover single dose-ranging in asthmatics	1-2i	90, 125,180, 200, 250	29	placebo, Primatene	(single doses)
B	Crossover high dose PK & safety in healthy	10i	1250, 1600	24	Primatene	(single doses)
B2	Crossover high dose PK & safety in healthy	10i	1250	23	Primatene	(single doses)
B3	Crossover high dose PK & safety in healthy	12i	1080, 1200	23	Primatene	(single doses)
C	Randomized parallel group in asthmatic adults & adolescents	2i QID	250	248	placebo, Primatene	12 weeks
C2	Safety extension of C	2i QID	250	134	placebo, Primatene	3 months
D	Randomized parallel group in asthmatic children	2i QID	250	35	placebo	4 weeks

*i = inhalations

All studies were conducted at least evaluator blinded. Randomization was not equal in Study C (and hence Study C2) but 4:1:1 E004:Primatene:placebo. The median age of patients receiving E004 in Study C was 37 and 60% were women. About 19% (76) were age 50 or older. The patients in the other studies were substantially younger.

COMMENT: The total exposure in these studies (numbers exposed and durations) is inadequate, barring catastrophic events, for detecting significant effects upon cardiac outcomes. For reassurances regarding the cardiac safety of E004 we are depending upon an absence of cardiac events in these low exposure studies, projections of minimal consequences of the immediate effects of E004 inhalation upon vital signs, and the benign post-marketing experience with Primatene.

Adverse Events in the Clinical Safety Studies

In these small, short duration clinical studies there were few concerning adverse events (AEs). There were no deaths. There was one serious AE (SAE) in Study C, an episode of acute bronchitis in a 58 year-old male on Primatene. There were two SAEs in Study C2, a pregnancy and breast cancer, both in the E004 arm. The episode of acute bronchitis would appear more likely related to the underlying asthmatic disease and, of course, the pregnancy and the breast cancer are highly unlikely related to E004.

The less serious AEs for E004 (and for Primatene) were ones that might be expected of an adrenergic agonist (i.e., tremor or “feeling jittery” and headache) or related to the underlying disease (e.g., cough, respiratory infections) with percentage rates typically in the single digits. Please see the primary reviews for discussions of these non-cardiac AEs. The AEs relevant to cardiac safety are tachycardia, hypertension, and chest pain or discomfort. These potential

cardiac AEs were not reported in the single-dose studies. We show the rates of these potential cardiac AEs in the repeat dosing clinical studies in Table 2.

Table 2: Patients with Potential Cardiac AEs in the Repeat Dosing Clinical Studies

	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

None of these potential cardiac AEs were SAEs or severe in intensity. One patient (discussed below) discontinued treatment for chest pain and tachycardia.

The chest pain/discomfort AEs are only potential cardiac AEs because other causes of chest pain, e.g., respiratory in this asthmatic population, are likely more common. The one patient with chest pain in Study C who discontinued is illustrative: A 22-year-od female patient in the E004 arm of Study C had AEs of "feeling of chest constriction post study drug inh" and "rapid heart beat heart palpitations" (and also "shakey") at visit 1 that led to discontinuation. Her heart rate by ECG was 58 at baseline, 71 at 2 minutes and 59 to 63 at 10 to 50 minutes. Her BP varied from 104/62 at baseline to 104/72 at 10 minutes. All ECGs were normal.

The most common term for the chest pain or discomfort was "chest tightness", although this was one of two choices on the CRF coding page for chest pain (angina was the other.) For example, a 43-year-old female in the E004 arm had three AEs of chest tightness, one of which was associated with wheezing. She had had albuterol prescribed for chest tightness. Her FEV1 improved temporarily with E004 inhalation but reverted to baseline by three hours when she reported the chest tightness. The available ECGs are normal. Her BP (SBP) did increase from normal at baseline (<120/90) to elevated post-inhalation (130-140/82-90). The other chest pain AEs were not serious or severe or noted as even possibly ischemic. The available post-inhalation ECGs from Study C did not document ischemia.

Regarding BP AEs, an elevated blood pressure (BP) AE at visit 1 in a 58-year-old female hypertensive patient in the Primatene arm of Study C led to the patient's discontinuation. Her BP increased from 161/98 at baseline to 184/105 at 60 minutes. Another patient in the Primatene arm of Study C, a 63-year-old female without a history of hypertension, had a hypertension AE at visit 2 that did not lead to discontinuation. Her baseline systolic values were high, about 135, with post-inhalation values reaching 164 (with diastolic 90). The CRF does not include values for visit 2. The investigator commented that the patient developed hypertension during the study and was referred to her primary doctor and prescribed lisinopril. We discuss the measured BP changes for all patients below.

Regarding tachycardia AEs, a 52-year-old female patient in the E004 arm of Study C had a tachycardia AE reported that lasted from 0500 to 1100 on a non-visit day. No other details are

provided. This patient's heart rates before and post-inhalation on visit 1 were low, all about 60 or lower. A 26-year-old male patient on E004 in Study C2 had "intermittent heart pounding post-dose up to 5 minutes" and a 51-year-old female patient on E004 in Study C2 had "'rapid pulse' post investigational product administration x 15 minutes, intermittent". None of these tachycardia AEs, or the palpitation AEs, were serious or severe. We discuss the measured heart rate changes for all patients below.

There were no arrhythmias reported as AEs other than the tachycardia. For the patients with increased heart rates the submitted ECGs document sinus rhythm, sometimes with a sinus arrhythmia, i.e., related to respiration. PVCs were not reported as AEs but the sponsor had three independent cardiologists review the ECGs for them. The rates of patients with PVCs were similar for E004 (1.4%), Primatene (1.6%), and placebo (1.0%). The E004 arm did have more incidences of PVCs. One patient accounted for seven incidences. Her narrative is as follows:

> "Subject . . . is a 35 year old Caucasian female with a history of asthma, seasonal allergic rhinitis, occasional headache and animal dander allergies and was enrolled T arm of Study C. She had a normal ECG at screening. At Visit 1, the subject's baseline ECG showed a single PVC with no accompanied symptom. Subject was dosed at 07:55 am with E004 study arm T. ECG measurements were conducted at 2, 10, 20 and 60 minutes post dose. At 2 and 60-minute post dose ECG readings did not show any appearance of PVCs. However, at 10 and 20 minute ECGs showed multiple PVCs with no accompanied symptoms. The subject's Visit 5 baseline ECG again showed a single PVC, the 2-minute ECG showed multiple PVCs, the 10-minute ECG showed a single PVC, the 20-minute showed no PVC and the 60-minute ECG showed multiple PVCs, all without any associated symptoms."

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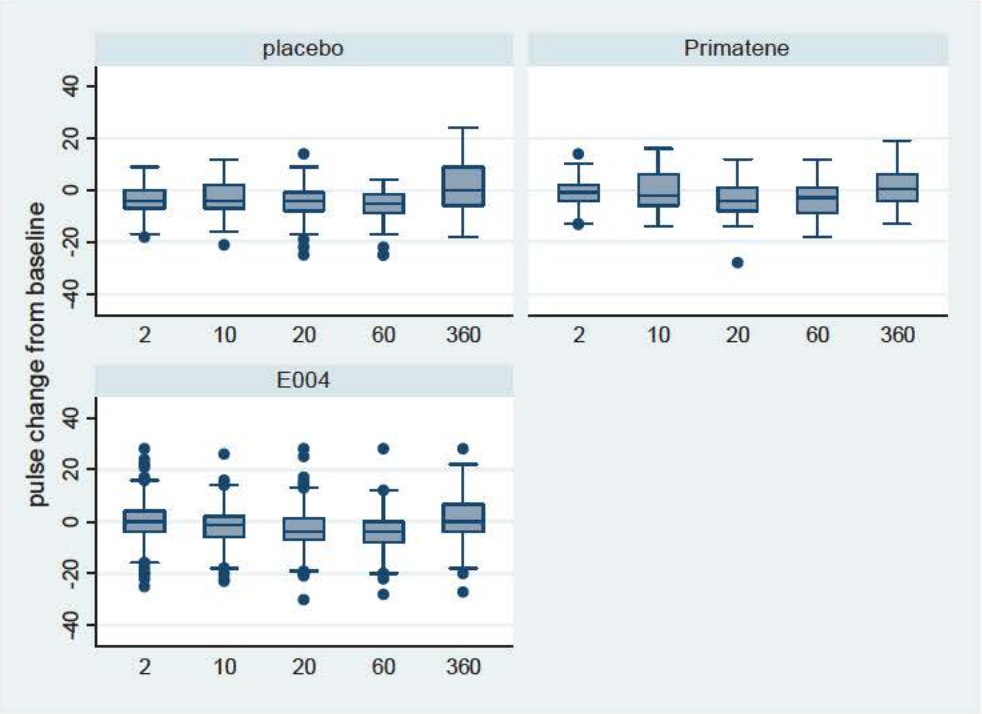
COMMENT: The chest pain AEs in these studies appear to be respiratory rather than cardiac in origin. The BP and tachycardia AEs are not concerning but the more revealing statistics regarding vital sign changes are the analyses of the measured vital signs below. The PVC cases are not alarming but neither do they eliminate the possibility that ventricular arrhythmias could be problematic in a vulnerable population, i.e., one with undiagnosed ischemic heart disease. As we discussed above, the exposures in the clinical studies were too low to provide absolute reassurance about the cardiac safety of E004.

Vital Signs in the Clinical Safety Studies

To-be-marketed Dose

At the proposed to-be-marketed dose there were little differences in average post-inhalation changes from baseline in vital signs in Study C for E004, Primatene, and placebo. We show box plots and tables of median and 95th percentiles of the changes from baseline by time post-inhalation at visit 1 in Study C for pulse rate in Figure 2, for SBP in Figure 3, and for DBP in Figure 4.

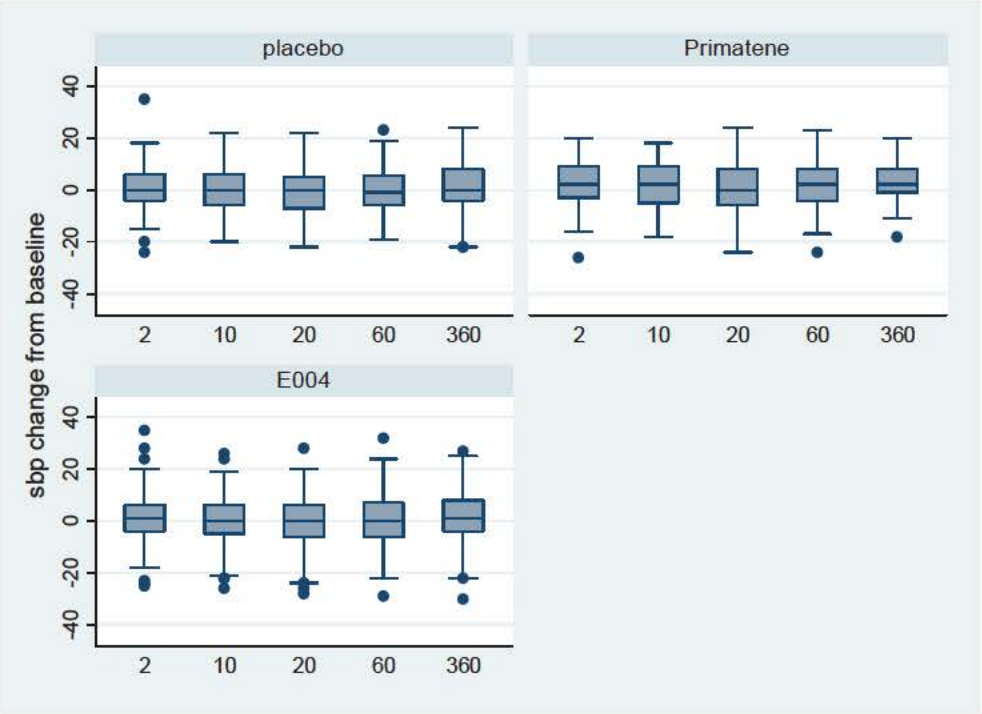
Figure 2: Pulse Rate Changes from Baseline by Minutes Post-Inhalation at Study C Visit 1



	E004				Primatene				placebo			
visit:	visit 1		visit 5		visit 1		visit 5		visit 1		visit 5	
minute	median	95th	median	95th	median	95th	median	95th	median	95th	median	95th
2	0	11	0	14	-1	9	0	13	-4	6	-2	7
10	-2	9	-1	11	-2	14	-1	7	-4	8	-2	11
20	-4	8	-3	7	-4	6	-3	10	-4	4	-4	6
60	-4	6	-4	10	-3	8	-5	12	-5	3	-4	8
360	0	15.5	1	16	0.5	14.5	2	19	0	16	1.5	16

95^{th} = 95^{th} percentile

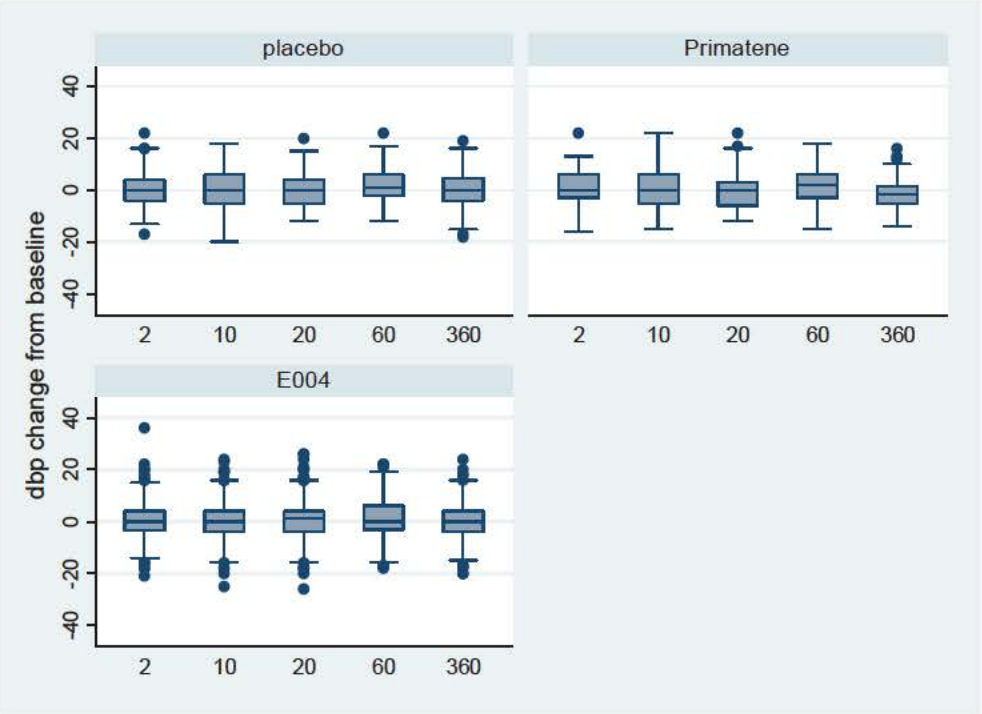
Figure 3: SBP Changes from Baseline by Minutes Post-Inhalation at Study C Visit 1



	E004				Primatene				placebo			
visit:	visit 1		visit 5		visit 1		visit 5		visit 1		visit 5	
minute	median	95th	median	95th	median	95th	median	95th	median	95th	median	95th
2	1	14	0	16	2	18	0	16	0	15	0.5	16
10	0	14	0	14	2	17	0	18	0	17	0	15
20	0	16	0	13	0	18	0	15	0	11	0	13
60	0	18	0	17	2	18	0	16	-1	17	0.5	16
360	1	15.5	1	16	2	14.5	2	19	0	16	1.5	16

95^{th} = 95^{th} percentile

Figure 4: DBP Changes from Baseline by Minutes Post-Inhalation at Study C Visit 1

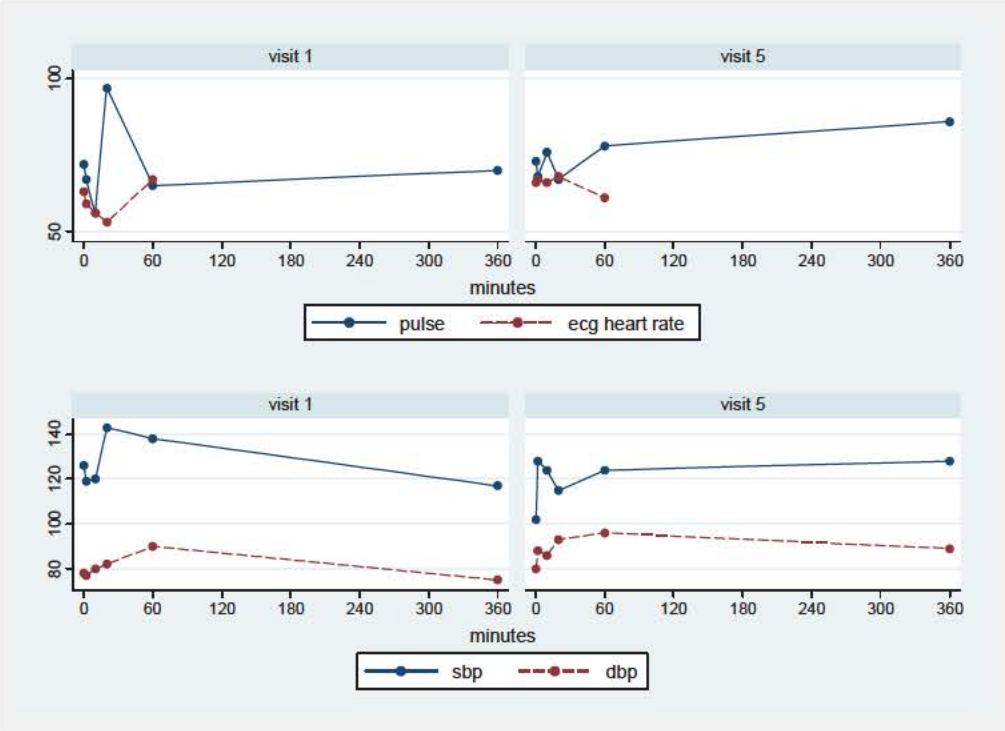


	E004				Primatene				placebo			
visit:	visit 1		visit 5		visit 1		visit 5		visit 1		visit 5	
minute	median	95th	median	95th	median	95th	median	95th	median	95th	median	95th
2	0	14	0	12	0	11	0	13	0	12	-0.5	14
10	0	14	0	14	0	14	0	10	0	15	0	10
20	0	14	0	14	0	16	1	13	0	11	0	13
60	0	15	0	15	2	12	0	15	1	16	0	14
360	0	15.5	0	16	-1.5	14.5	1	19	0	16	0	16

95^{th} = 95^{th} percentile

Results for visit 5, the end-of-study visit at which post-inhalation vital signs were also recorded, are similar. While the box plots suggest that there were little differences in vital sign changes from baseline at visit 1 in Study C, whether there are more outliers with E004 is more difficult to judge because of the 4:1:1 randomization and the noisiness of the data. The noisiness of the data is illustrated well by the not uncommon differences between the pulse rate recorded as a vital sign and the heart rate from the ECGs. While the median difference in changes from baseline minutes 2-10 is only about 3 bpm, the variability is high, e.g., the 5^{th} percentile is -16 and the 95^{th} percentile 9. We show an example of such differences for one E004 patient from Study C in Figure 5.

Figure 5: Example of Differences between Pulse and ECG Heart Rates in Study C

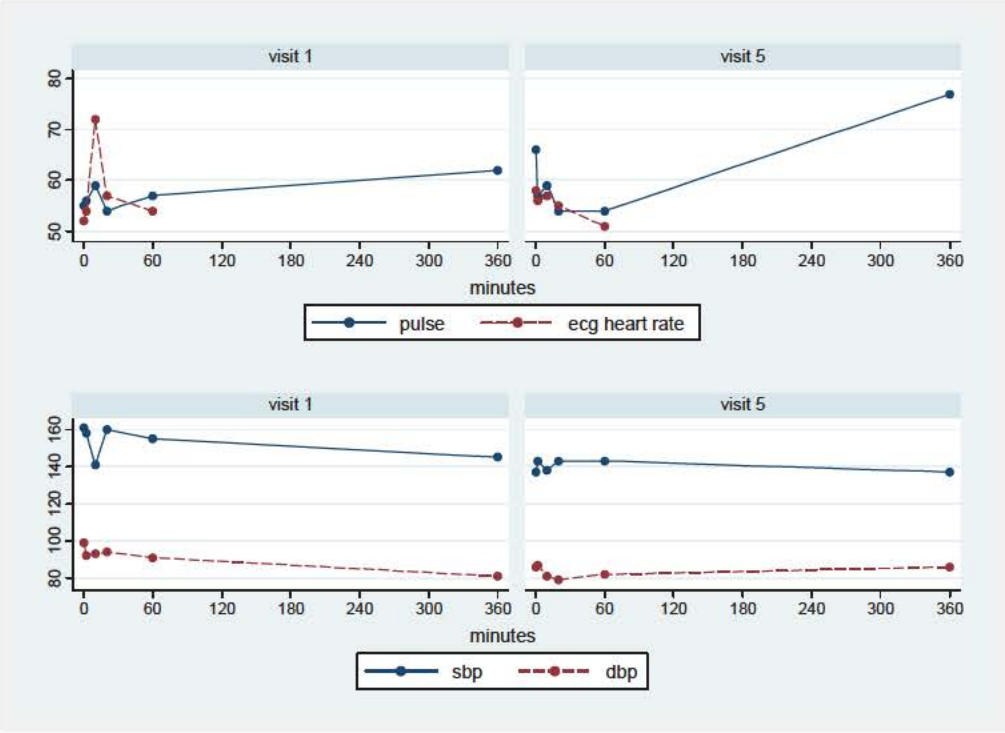


The high pulse rate at 20 minutes in visit 1 in Figure 5 seems spurious. While there were increases in SBP of about 20 mm Hg 2 to 20 minutes after inhalation of E004 for this patient at both visits, it is unclear whether this is a drug effect or due to activity differences because, while the increase was transient at visit 1, SBP stayed within normal limits at visit 5 and the BP increase was sustained through 360 minutes.

We examined the vital sign patterns over time for patients in Study C with increase in pulse or heart rate of 20 bpm or more (11 E004 and 3 placebo) and for SBP of 25 mm Hg or more (5 E004 and 1 placebo). The numbers of these outliers are consistent with the 4:1:1 randomization.

Regarding the patients with outlier heart rate increase, the three placebo patients who showed a heart rate increase of 20 bpm or more at visit 1 did not show a similar increase at visit 5. We show the vital sign patterns for one of these patients, a 52-year-old female, in Figure 6.

Figure 6: Heart Rate Increase at Visit 1 in a Study C Placebo Patient

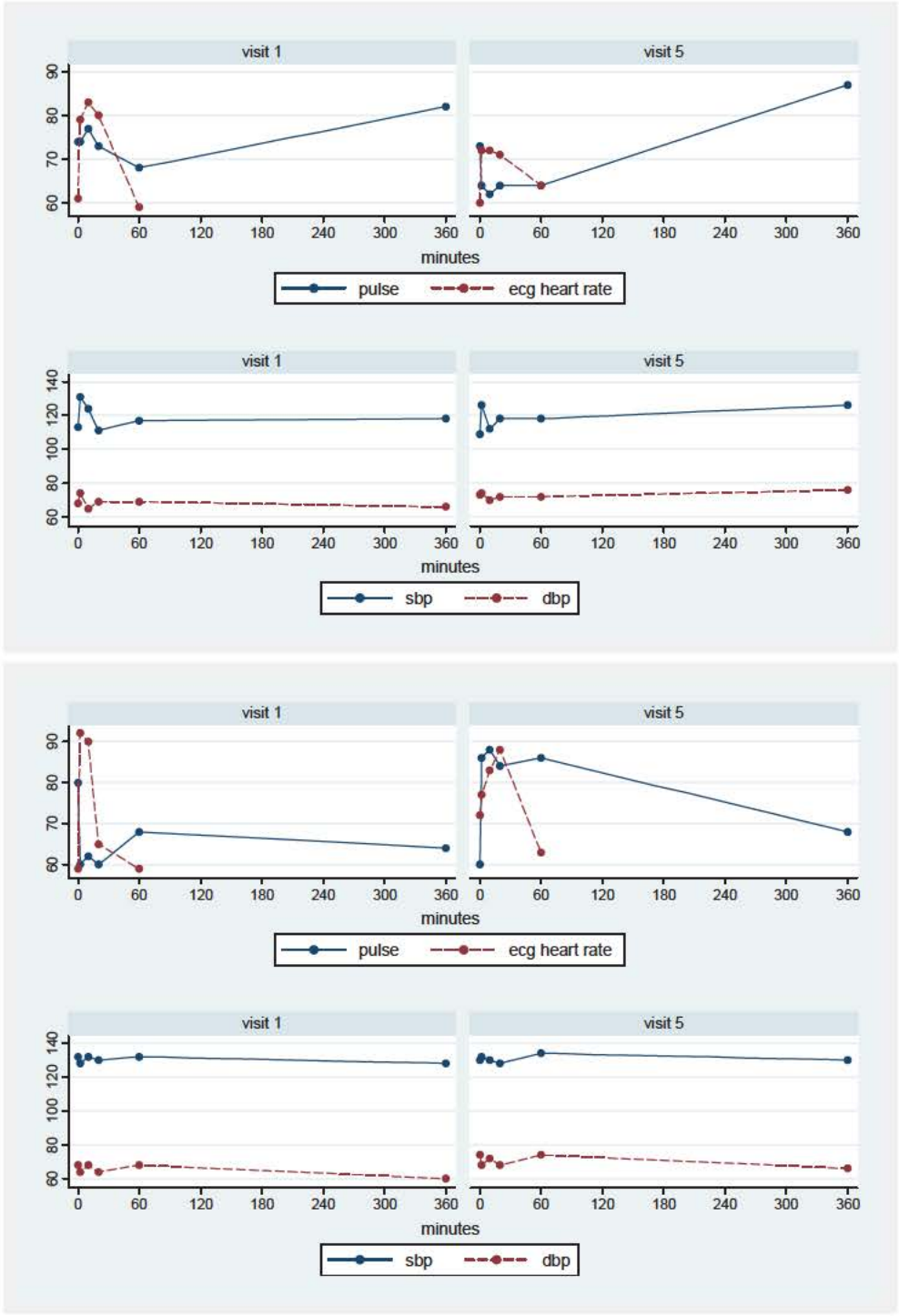


Note that this patient has systolic hypertension. The heart rate changes in the other two placebo patients were similar. None of them discontinued. We can not determine whether the heart rate increases at visit 1 represent anxiety or an acute effect of HFA propellant, although we might expect the latter to be seen at visit 5 as well.

Four E004 patients with heart rate increase of 20 bpm or more at visit 1 discontinued. They were a 17-year-old female for pregnancy, a 44-year-old male for throat irritation, a 21-year-old female for burning sensation, and a 26-year-old female for a new job—i.e., no one discontinued for the heart rate increases or cardiac complaints. For all but the last the heart rate changes by pulse and ECG were inconsistent. For the first the heart rate reported by ECG was increased but the quality of the ECGs reported as high heart rate were abysmal and the non-increased pulse rates were likely accurate. For the last the ECGs showed an increase from 62 at baseline to 82 at 2 minutes with return to baseline by 20 minutes.

For the E004 patients with heart rate increases of 20 bpm or more at visit 1 who did not discontinue the increases were usually not replicated at visit 5. We show the vital sign patterns for the two patients with the most consistent results at visits 1 and 5 in Figure 7.

Figure 7: E004 Patients with Similar Increases in Heart Rates at Study C Visits 1 and 5

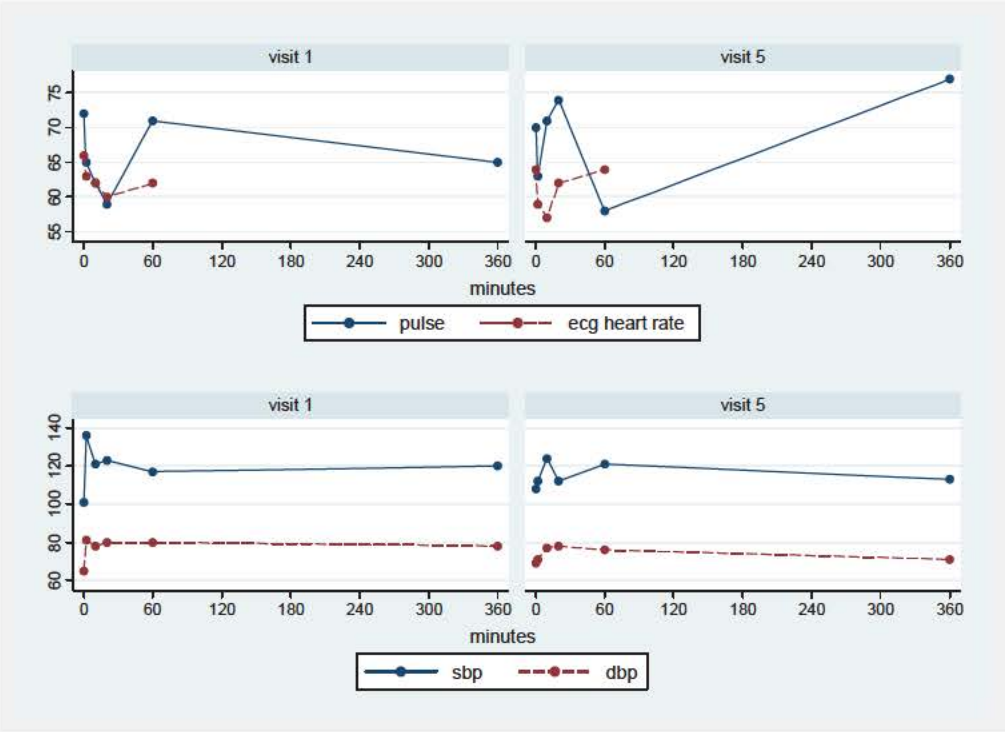


Neither patient with the heart rate increases shown in Figure 7, the first a 26-year-old male and the second a 56-year-old female, reported any AEs at any visit.

The patients who appeared to have real increases in heart rate immediately post-inhalation at visit 1 had lower baseline heart rates, i.e., about 60 or lower, than the other patients (mean about 66). The increases remained well within normal limits, i.e., much <100 bpm.

Regarding blood pressure increases, no patient with an increase in SBP of 25 mm Hg or more at visit 1 had a substantial elevation at visit 5. None of these patients discontinued. We show the vital sign changes for the placebo patient with such a SBP change in Figure 8.

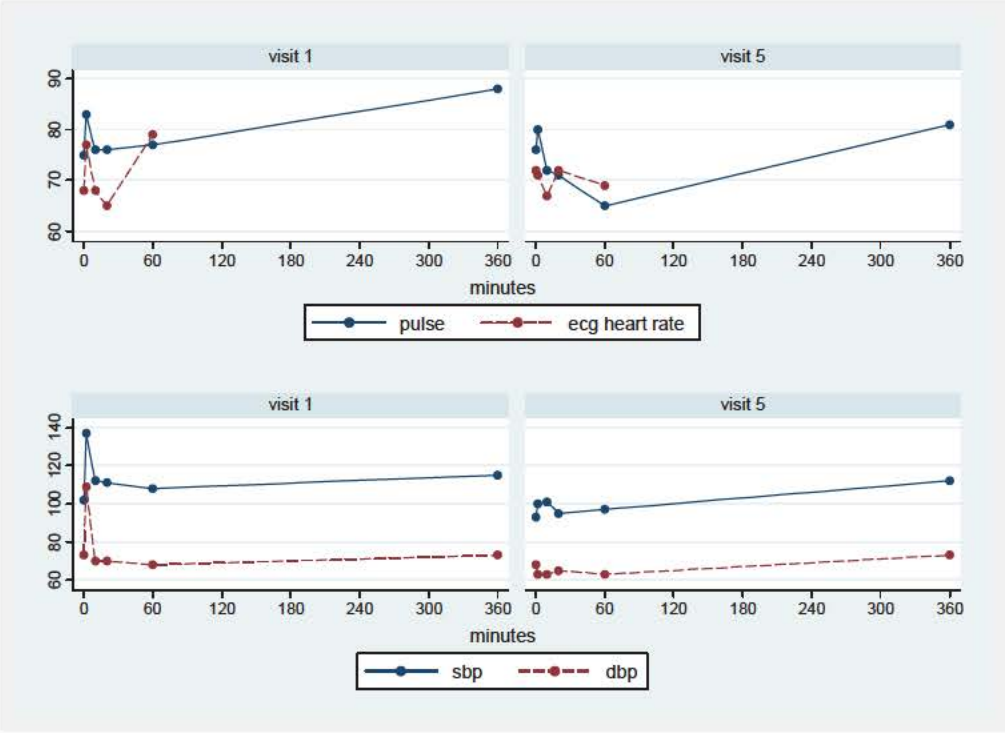
Figure 8: Placebo Patient with SBP Increase ≥ 25 mm Hg at Study C Visit 1



The large SBP increase in the placebo patient at visit 1 as shown in Figure 8 appears to be related to an unusually low baseline value (median SBP for this patient was about 119). This patient does appear to show a modest increase in BP immediately post-inhalation that is similar between visits 1 and 5.

We show the vital sign changes for the E004 patient with the most consistent BP changes in Figure 9.

Figure 9: E004 Patient with SBP Increase ≥ 25 mm Hg at Study C Visit 1



The patient whose vital signs we show in Figure 9 was a 12-year-old male. He reported "tremulousness" throughout the study. No other patient with a 25 mm Hg or greater increase in SBP at visit 1 had AEs reported except for one AE of elevated bilirubin.

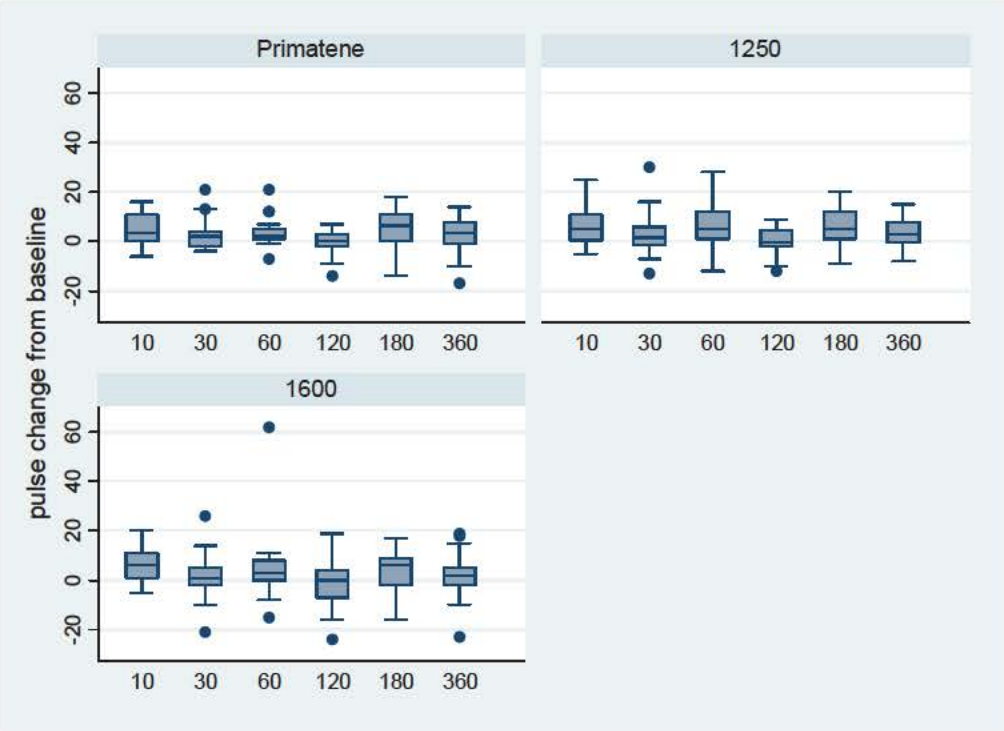
COMMENT: The changes in vital signs post E004 inhalation at the proposed to-be-marketed dose appear to be modest. The major limitation of the studies is that the data are very noisy, a limitation that could obscure larger vital sign changes in some patients.

High Dose

The high dose PK/safety studies in normal volunteers should have been useful in estimating a dose/response relationship between dose and heart rate and BP effects. However, we would expect the effects on heart rate and BP to be closely related to the epinephrine levels shown in Figure 1, i.e., within the first 15 minutes post-inhalation. The vital sign plots in the preceding To-be-marketed Dose section confirm that any drug-related effects on vital signs appear early. Unfortunately, of the high dose Studies B, B2, and B3, only Study B measured vital signs before 30 minutes post-inhalation (at 10 minutes). We analyze the vital sign changes for Study B below.

We show box plots and tables of median and 95th percentiles of the changes from baseline by time post-inhalation and treatment in Study B for pulse rate in Figure 10, for SBP in Figure 12, and for DBP in Figure 13.

Figure 10: Pulse Rate Changes from Baseline by Minutes Post-Inhalation in Study B

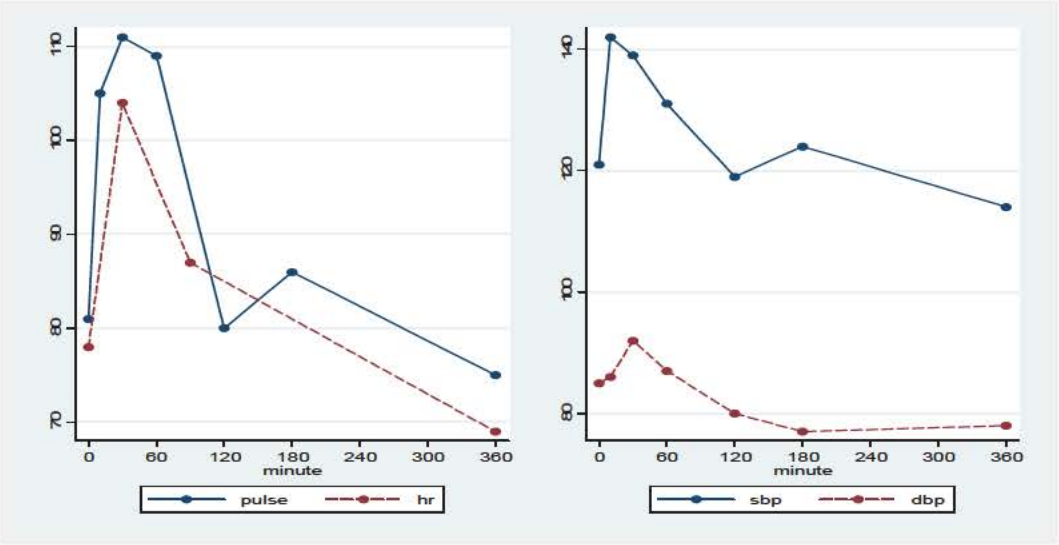


	Primatene 2200 mg		E004 1250 mg		E004 1600 mg	
minute	median	95th	median	95th	median	95th
10	4	13	5	24	6	18
30	2	13	2	16	1	14
60	2	12	5	21	3	11
120	0	6	-1	8	0	8
180	7	15	5	17	6	15
360	4	13	3	10	2	18

95^{th} = 95^{th} percentile

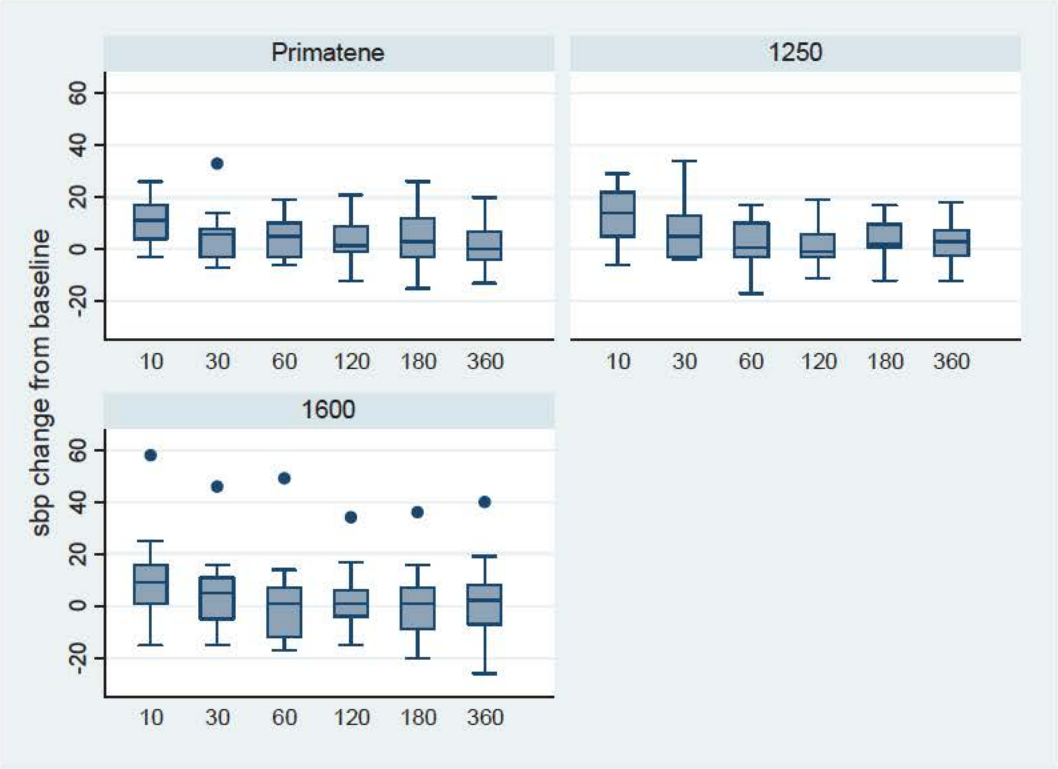
The patient with the >20 bpm increase in pulse rate at 30 minutes post inhalation of E004 1250 mg was a 20-year-old female. Her heart rate increases were consistent by pulse and ECG and accompanied by substantial BP increases—see Figure 11. However, while she had a similar increase in pulse rate with Primatene, the ECG heart rate increase was modest and her BP decreased slightly. Prior to the E004 1600 dosing she had an "upset stomach" and the site reported that she was upset about not having transportation home, vomited, and felt better. Both her heart rate and blood pressure fell substantially by 30 minutes. Her sequence was control 1250, and then 1600.

Figure 11: Vital Signs after E004 1250 mg Inhalation for the Patient with >20 BPM Increase in Pulse Rate at 30 Minutes in Study B



The patient with the reported >60 bpm increase in pulse rate at 60 minutes post-inhalation of 1600 mg was a 19-year-old male with a baseline pulse rate of 55 and BP 108/55. His BP at 60 minutes was 96/70 and no AEs were reported for this visit. His pulse rate at 30 minutes was reported as 81 (increased 21 from baseline) while his ECG heart rate at 30 minutes was 62 without abnormalities or extra beats.

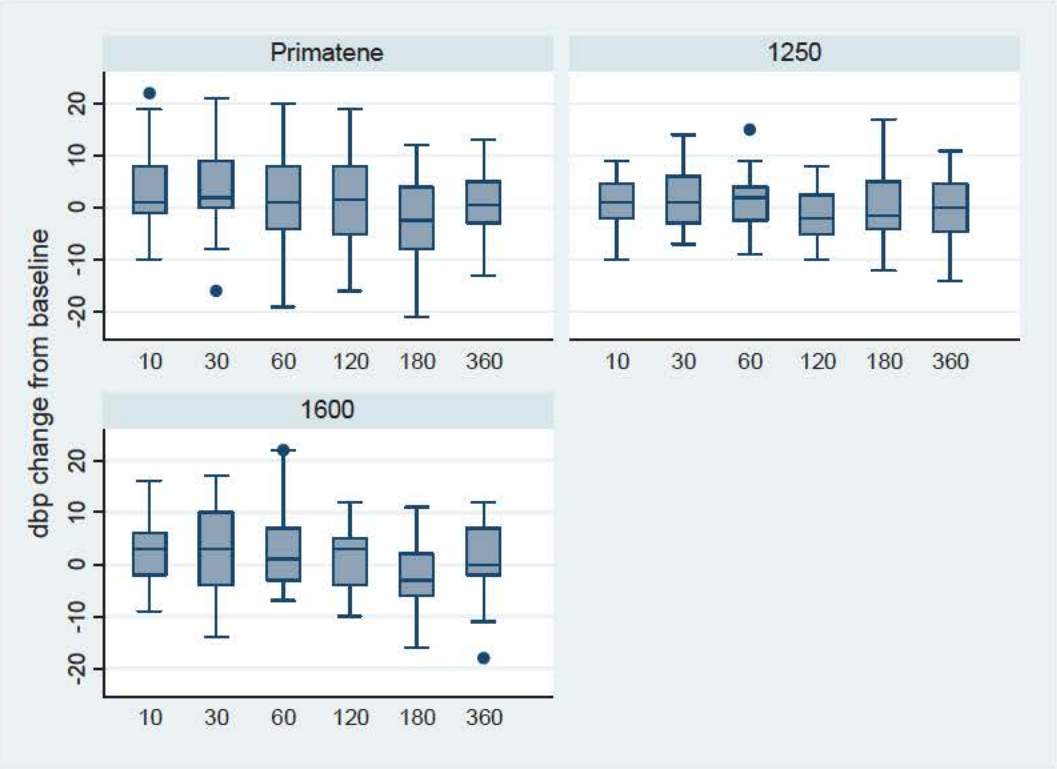
Figure 12: SBP Changes from Baseline by Minutes Post-Inhalation in Study B



	Primatene 2200 mg		E004 1250 mg		E004 1600 mg	
minute	median	95th	median	95th	median	95th
10	11	22	14	24	9	25
30	6	14	5	18	5	16
60	5	18	1	13	1	14
120	2	15	-1	18	1	17
180	3	16	2	17	1	16
360	0	15	3	17	2	19

95^{th} = 95^{th} percentile

Figure 13: DBP Changes from Baseline by Minutes Post-Inhalation in Study B



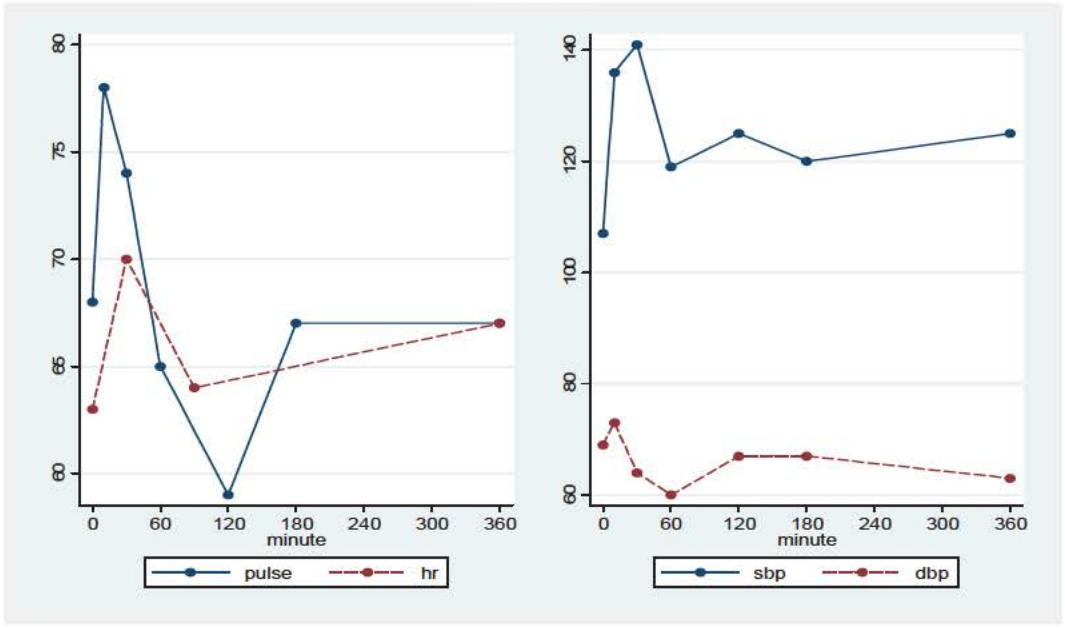
	Primatene 2200 mg		E004 1250 mg		E004 1600 mg	
minute	median	95th	median	95th	median	95th
10	1	19	1	9	3	14
30	2	15	1	13	3	16
60	1	14	2	9	1	15
120	2	12	-2	7	3	12
180	-3	9	-2	10	-3	10
360	1	11	0	8	0	9

95^{th} = 95^{th} percentile

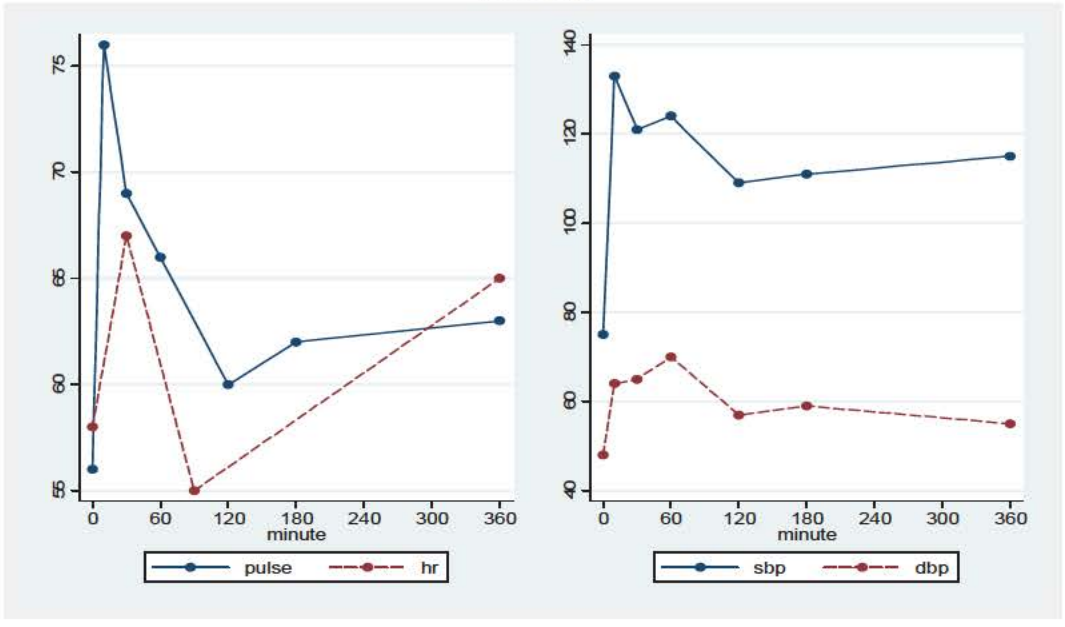
We show the vital sign changes for the patient with reported >50 mm Hg increase in SBP at 10 minutes after E004 1600 mg inhalation in Study B in Figure 14. The extreme increase appears exaggerated by a low baseline BP because this patient's usual SBP appears to be about 110-120 rather than the 75 reported as baseline prior to the E004 1600 mg inhalation. The true increase appears to be about 30 mm Hg rather than 58. This patient had similar increases in SBP after 1200 mg inhalation.

Figure 14: Vital Signs after E004 Inhalation for the Patient with >50 mm Hg Increase in SBP at 10 Minutes in Study B

1250 mg



1600 mg



COMMENT: The Study B results suggest that SBP and heart rate increases following high E004 dosing (5x the proposed to-be-marketed dosage) can be substantial in some patients. These increases are relevant to the overdose or abuse situation. Conversely, they confirm that the BP and heart rate changes expected with the proposed to-be-marketed dosage are modest.

Postmarketing Experience

Literature Review

The sponsor found very few reports of AEs with Primatene or epinephrine inhalation in PubMed and ISI. Regarding studies, they summarized several published papers for pediatric populations. They claim that results of these pediatric studies showed that increases in heart rate and BP were reported in patients who were given 4 mg or 5 mg of nebulized epinephrine (1 mg/mL), but there was no significant changes for patients receiving a 3 mg dose. Regarding SAEs, they found only four case reports. All of the SAEs occurred with abuse, overdose, or inappropriate use (the latter a case of injection of the Primatene solution extracted from an inhaler.)

COMMENT: Our PubMed searches confirmed the paucity of reports. While we don't agree that the data conclusively prove a 3 mg threshold for CV effects regardless of the inhalation device, we judge that the NDA clinical studies support that CV effects of E004 are modest at the to-be-marketed dose and unlikely to produce SAEs in patients without overt cardiac disease.

AERS Database

The sponsor analyzed reports from the AERS database of post-marketing reports for both Primatene and albuterol inhalers. They also compiled sales statistics from IMH Health. We have reproduced the most relevant tabulation regarding cardiac safety in Table 3.

Table 3: Sponsor's CV AEs reported to the FDA from 1997 to 2012 for Primatene and Albuterol Inhalers

ADEs	Primatene® Mist		Albuterol Inhalers		Ratio of ADE Rates Z_2/Z_1
	# of ADE Reports in the FAERS Databases	ADE Rate, # of ADE per 1 Million Units,	# of ADE Reports in the FAERS Databases	ADE Rate, # of ADE per 1 Million Units,	
Heart Rate Increased	15	0.2	642	0.9	4
Myocardial Infarction	13	0.2	567	0.8	4
Blood Pressure Increased	6	0.1	471	0.7	7
Palpitations	6	0.1	645	0.9	10
Cardiac Arrest	5	0.1	336	0.5	6
Hypertension	5	0.1	553	0.8	10
Hypotension	3	0.0	581	0.8	18
Total	53	0.8	3,795	5.2	7

The sponsor alleges that the rates of post-marketing CV AEs are lower for Primatene than for albuterol inhalers.

COMMENT: Our analyses of the AERS database using the Empirica Signal data mining software (which we summarized briefly under Background above) are consistent with the sponsor's AERS analyses. The post-marketing reports for Primatene are not concerning.

Missing or Incomplete Data or Analyses

In general the completeness of the NDA submission is very good: The datasets submitted appear complete and accurate. The submission includes complete CRFs as well as ECGs. We used all of these to try to delineate the cardiac risks of E004 and found them informative. We are also not concerned with missing or incomplete analyses because, given the apparently complete data sets, we were able to perform the analyses we considered appropriate (within the limitations of the study designs and conduct discussed next.)

There are limitations relevant to missing or incomplete data for both the study designs and conduct:

- Regarding study design, for the high dose studies vital signs were not recorded early around T_{max}. As documented above, there are some patients who showed substantial increases in BP and heart rate and the earliest (30 minute) post-inhalation vital sign recordings. Vital signs were recorded earlier in some of the lower, repeat dosing studies, but the latter have problems with conduct as we discuss next.

- Regarding study conduct, the vital sign measurements appear to be very noisy as we documented above regarding the discrepancies between pulse rate and heart rates evaluated by ECG. The vital sign measurements do not appear to be biased towards the null because all of the extreme increases for both pulse and SBP appear related to unusually low baseline measurements rather than dangerously concerning drug-related increases. However, we do have concerns that the noisy data may have obscured some drug-related effects. Multiple baseline measurements and careful measurements for the first hour post-inhalation with patients at rest would have provided better estimates of drug effect upon vital signs.

While there were the above limitations regarding study design and conduct, we believe that the studies and vital sign data are adequate for providing some reassurance about the cardiac safety of E004 at the proposed to-be-marketed dose. The major limitation regarding having complete confidence about the cardiac safety of E004 is the lack of a large, cardiovascular outcome study exposing a sufficiently diverse patient population corresponding to the expected use post-marketing. However, given the relatively unconcerning findings in the clinical studies submitted, we do not recommend requiring such an outcome study at this time.

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/s/

THOMAS A MARCINIAK
12/05/2013

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12/05/2013