U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CONSUMER BEHAVIOR STUDIES

NDA/BLA #:	NDA205920
Supplement #:	Not Applicable
Drug Name:	(b) (4) 125 mcg/inhalation (Epinephrine Inhalation Aerosol USP)
Indication(s):	(b) (4)
Applicant:	Amphastar
Date(s):	Date re-submitted: 06/28/2016 PDUFA due date: 12/28/2016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
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Tertiary Reviewer:	Mark Levenson, Ph.D., (Acting) Division Director
Main Review Division:	OND/ODEIV/DNDP
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Project Manager:	Tinya Sensie
Keywords:	Label comprehension studies; Human factor studies

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2 LIST OF ACRONYMS

ALHFQ	Additional Labeling Human Factor Questions
AR	Acceptable Rate
CBT	Critical Behavioral Tasks
CI	Confidence Intervals
CRL	Complete Response Letter
DFL	Drug Fact Label
HF	Human Factor Study
IFU	Instruction For Use
ITPP	Intent-to-participate Population
LCS	Label Comprehension Study
MDI	Metered Dose Inhaler
OD	Original Datasets
OTC	Over-the-counter
PI	Package Insert
RBED	Risk-based Evaluation Datasets
REALM	Rapid Estimate of Adult Literacy in Medicine
REALM-Teen	Rapid Estimate of Adolescent Literacy in Medicine
SABA	Short-acting beta2-agonist
TEP	Task Evaluable Population

1 EXECUTIVE SUMMARY

This is a statistical review of an NDA resubmission for epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA) dispensed using a metered dose inhaler (MDI). Epinephrine-HFA is a short-acting beta2-agonist (SABA) bronchodilator used as a quick relief medication for acute bronchospasm. The proposed indication is for over-the-counter (OTC) use in the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath.

This statistical review evaluates the consumer behavior studies submitted in this NDA. Those are three label comprehension studies (LCS IV, LCS V and LCS VI) and one human factor study (HFS). The Applicant conducted these studies to address deficiencies identified by FDA in a complete response letter (CRL) on 5/22/2014 in response to previous submission of the NDA on 7/22/13. This review did not evaluate other consumer behavior studies conducted under this NDA in the earlier submission.

The three label comprehension studies evaluated whether consumers could understand the information on the proposed Drug Facts Label (DFL) and package insert (PI). Each of the three LCS enrolled more than 450 subjects (16 years of age or older) from multiple retail sites. The Applicant used iterative testing in which results from each LCS led to changes in labeling (DFL and PI) further tested in subsequent LCS.

In each LCS and comprehension objective, the Applicant assessed comprehension relative to the performance threshold of 85% for the general population. Thus, a study meets a communication objective if the lower bound of the 95% confidence interval of the comprehension rate exceeds 85%. LCS IV focused on subject comprehension of instructions for washing, priming, re-priming and using the device. All the comprehension objectives were met in LCS IV except the one for "priming the inhaler when wet or not used for 2 days". Thus, the label was revised and this latter comprehension objective was tested again in LCS V. This objective was still not met in LCS V, so the label was further revised and the objective was tested again in LCV VII where it was met. In addition, LCS V tested and met the objective for the prime before first use and place finger on center of dose indicator.

In LCS IV, LCS V and LCS VI, specific subject comprehension levels met the 85% threshold for the general population after the label was revised based on prior studies After all label revisions, the comprehension rate still fell below the 85% threshold in low literacy subjects for the following evaluation objectives:

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

The human factor study was conducted in 151 subjects (>12 years old) from two sites. This study assessed consumers' ability to carry out three tasks related to use and maintenance of the MDI: First use (task 1), Cleaning (task 2) and Routine Use (Task 3). Correct completion rates were 85% or lower for each task. More specifically, completion rates and 95% confidence interval are 70% (62%, 77%) for first use task, 60% (52%, 68%) for cleaning task, and T 85% (78%, 90%) for

routine use task. When correct completion rates included not only performance coded as completed but also performance coded as completed with issues, as in Applicant's analyses, 95% confidence interval for each task was higher than 85%.

In addition to behavior tasks, the human factor study assessed understanding level of the labeling on three different items: (i) Dose Indicator, (ii) Dropped Device and (iii) Hold Inhaler Properly. The study met comprehension objectives on all the label comprehension items with correct comprehension rate significantly above 85% on each item.

Subgroup analyses in the human factor study showed that subjects with the following characteristics did not perform as well in all tasks (i) a very short reading time of E004 IFU (instruction for use), (ii) low literacy level, and (iii) carryover habit of prior inhaler experience.

The reviewer recommends that additional instructions about priming should be included in the Instructions for Use (IFU). The instructions for use of "Prime the inhaler again if it is wet or not used in 2 days" was difficult to understand relative to other tested messages in the label comprehension study. Comprehension rates for this instruction did not exceed 85% in LCS IV, LCS V but did exceed 85% in LCS VI. Although the PI and DFL were revised, the IFU was not revised. The reviewer believes that the additional instructions should be included in the IFU, so that potential consumers can safely use the product.

2 INTRODUCTION

This is a statistical review of new consumer behavior studies in an NDA resubmission for epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA). The drug is dispensed using a metered dose inhaler (MDI) with a dose of 125mcg/inhalation. Epinephrine-HFA is a short-acting beta2-agonist (SABA) bronchodilator used as a quick relief medication for acute bronchospasm. The proposed indication is for over-the-counter (OTC) use in the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath.

Epinephrine-HFA MDI is proposed 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. Proper use of the device includes shaking at every use, cleaning every day and priming frequently. The device must be shaken immediately prior to dosing because the product is a suspension and settling may occur if the device is not shaken. The device also requires cleaning by disassembling the device and washing with warm water on a daily basis. Priming is required at first ever use, first use in 2 days or more of no-use, after cleaning if it is wet, or after dropping device.

Instructions of use also include how to properly use the dose indicator. The epinephrine HFA MDI includes a top mounted dose actuation indicator. This device attaches to the end of the drug product canister using an adhesive label. The dose indicator mechanically counts each actuation. The display advances every 10 actuations and is labeled numerically in increments of 20. When 20 or fewer actuations remain, the display begins to turn red in color. The red zone continues to fill the display until the counter indexes to zero. At this point the display is at the zero count and completely red, indicating the need to replace the inhaler. After the zero count has been reached, additional actuations of the MDI no longer advance the display. Instructions also note that if the MDI is dropped, the dose indicator is no longer reliable and patients must keep track of the number of sprays taken. The package instructions note that a finger must be placed on the center of the dose indicator during actuation.

The application contained three label comprehension studies (LCS) and a human factor study, The Applicant conducted the three LCS to evaluate whether consumers could understand the information on the proposed Drug Facts Label (DFL) and package insert (PI). After the Applicant determined that the label comprehension studies showed an adequate consumer understanding of the labeling, the human factor study was performed. In the human factor study, subjects were instructed to actually demonstrate how to use the product, based upon the labeling.

This statistical review will address the consumer behavior studies, specifically the label comprehension and human factor studies, submitted in this NDA.

Regulatory history

Epinephrine, one of the first sympathomimetic agents in medicine, has been marketed in the United States in a variety of different formulations since 1901, with use in the treatment of asthma dating back to the early 1900s. Epinephrine in an MDI formulation utilizing CFCs (Primatene® Mist) was approved for OTC use for the treatment of symptoms of asthma in 1967. Beginning in

1996, MDIs using CFC propellants began to be phased out to protect the environment under the Montreal Protocol. FDA published the Final Rule in 2008 and based upon a request from the manufacturer, the end date (effective date) for use of CFCs for epinephrine MDIs was December 31, 2011.

The FDA and sponsor met several times to discuss which consumer behavior studies are needed and what they should test. Please refer to Statistical Review by Scott Komo on 4/25/2014 for a detailed review of the regulatory history.

On 4/8/2013, the Applicant submitted an NDA (under NDA 205496) that the Agency refused to file due to a number of deficiencies that did not allow a substantive review. The NDA was resubmitted on 7/22/13 (under NDA 205920). The NDA contained three label comprehension studies and a human factor study. FDA reviewed the submission and sent the Applicant a complete response letter (CRL) on 5/22/2014 outlining multiple deficiencies. The letter states that the application could not be approved due to the failure to establish the product usability in the OTC setting. The following study deficiencies were included:

- The label comprehension studies identified limitations in consumers' understanding of the following critical information: the need to prime the inhaler before using the first time, the need to clean the product daily after use, and the need to re-prime when wet, and not relying on the indicator if dropped.
- The human factor study did not assess whether consumers understood the need to initially prime and clean the product without prompting. The study did not provide sufficient information to assess whether cleaning and use of the device was performed appropriately. In addition, the human factor study did not adequately assess consumers with low literacy.

The NDA was resubmitted on 6/28/16 (under NDA 205920) to address these deficiencies. As stated above, the NDA contains new label comprehension studies and a new human factor study. A consumer behavioral actual use study, which collected device performance data, was not conducted. This review will focus on reviewing the studies submitted in this application and will not review studies submitted in the previous application.

2.1 Overview

The consumer studies submitted in the application are presented in Table 1.

Table 1: List of all studies included in the review

Applicant defined study number	Study Type	Number of subjects	Number of low literacy (%)
LCS IV	Label Comprehension	506	126 (25%)
LCS V	Label Comprehension	492	113 (23%)
LCS VI	Label Comprehension	485	98 (20%)
HF G3	Human Factor	151	24 (16%)

Source: The reviewer's table

2.2 Data Sources

List of materials used in this review along with the locations are listed in Table 2.

Table 2: List of review materials and locations

Applicant defined study number	Document type and name	Location
LCS IV	Study Protocol and Study Report	\\cdsesub1\evsprod\NDA205920\0037\m1\us
	Analysis Datasets: **adcomp.xpt; addemog.xpt; survey.xpt**	\\cdsesub1\evsprod\NDA205920\0037\m5\datasets\lc-f4\analysis\legacy\datasets
LCS V	Study Protocol and Study Report	\\cdsesub1\evsprod\NDA205920\0037\m1\us
	Analysis Datasets: **adcomp.xpt; addemog.xpt; survey.xpt**	\\cdsesub1\evsprod\NDA205920\0037\m5\datasets\lc-f5\analysis\legacy\datasets
LCS VI	Study Protocol and Study Report	\\cdsesub1\evsprod\NDA205920\0037\m1\us
	Analysis Datasets: **adcomp.xpt; addemog.xpt; survey.xpt**	\\cdsesub1\evsprod\NDA205920\0037\m5\datasets\lc-f6\analysis\legacy\datasets
HF G3	Study Protocol, Statistical Analysis Plan and Study Report	\\cdsesub1\evsprod\NDA205920\0037\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\amp-2016-e004-g3
	Analysis Datasets: **basic.xpt; demo.xpt; task1*-task6.xpt; task1od.xpt; task1rbd.xpt**	\\cdsesub1\evsprod\NDA205920\0037\m5\datasets\g3\analysis\legacy\datasets \\cdsesub1\evsprod\NDA205920\0042\m5\datasets\g3\analysis\legacy\datasets \\cdsesub1\evsprod\NDA205920\0042\m5\datase

Applicant defined study number	Document type and name	Location
		ts\g3\analysis\legacy\datasets

Source: The reviewer's table.

*Our review found that one table submitted by the Applicant could not be reproduced by using the submitted datasets, and per our request the Applicant resubmitted two revised datasets: task1od.xpt and task1rbd.xpt.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and reports of this submission were submitted electronically. The data and analysis quality are adequate as it allowed us to reproduce most key safety findings and conduct additional analyses. The datasets were well documented in the define.pdf files. We could not originally reproduce one table in HF G3 study report by using the originally submitted datasets (task1*-task6.xpt). After an information request to Applicant, on July 25th, 2016 we received two revised datasets: task1od.xpt and task1rbd.xpt where we could reproduce the results.

3.2 Label Comprehension Study IV

The objective of this LCS was to evaluate the package insert for Epinephrine Inhalation Aerosol USP, and to test for consumer comprehension of the E004 instructions that differ from the already approved Primatene® Mist product.

The primary objectives of this study were to determine if participants understand the following messages from the package insert:

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 2 days

4) Place finger(s) on center of dose indicator.

5) Remove the canister for cleaning mouthpiece.

6) Do not use in children under 12 years of age.

7) Do not use more than 8 inhalations in 24 hours.

8) See your doctor if you have more than 2 asthma attacks in a week.

The secondary objective was to determine if participants understand:

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

3.2.1 Study Design

This was a multi-center consumer label comprehension study designed to determine the effectiveness of the E004 package insert information. Participants consisted of adults 16 years of age and older selected from the general population at seven retail sites across the United States, of whom approximately 25% would be identified as low literacy as defined by the Rapid Estimate of Adult Literacy in Medicine (REALM) Test or the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen), depending on the age of the participant.. All subjects answered comprehension questions about the proposed package insert.

The Applicant enrolled 506 subjects in this LCS IV at seven US retail sites as listed in Table 3.

Table 3: List of study sites-LCS IV

Site ID	Name	Frequency	Percent
1022	Chicago Ridge Mall, Chicago Ridge, IL	72	14%
2020	White Marsh Mall, Baltimore, MD	92	18%
3010	Sugarloaf Mills, Lawrenceville, GA	79	16%
3080	Citrus Park Mall, Tampa, FL	92	18%
4011	Colorado Mills Mall, Lakewood, CO	52	10%
4022	Mainplace Mall, Santa Ana, CA	51	10%
4070	Kitsap Mall, Silverdale, GA	68	13%

Source: The reviewer's table.

3.2.2 Endpoints

Table 4 below lists all communication objectives that were tested in this study along with the corresponding target threshold for each objective. All primary and secondary communication messages were assessed as primary or secondary endpoints, respectively.

The thresholds for the primary endpoints are set at 85% by the Applicant. Failure to understand primary objectives 1-5 could lead to malfunction. Most often, malfunction would lead to lack of effectiveness (under-dose) and more rarely to possible safety issue (over-dose under certain conditions of misuse). Failure to understand primary objectives 6-9 could lead to safety issues. Objective #2 was planned but never included in the study for further testing.

Failure to understand instructions in the secondary objective are not as critical as first objective. An in-vitro laboratory study showed that falling would not cause critical malfunctions of the device, but occasionally the dose indicator would advance by one count. (b) (4) the Applicant argued that the risk of dose indicator being damaged during dropping as having an impact to the safety is mitigated. Therefore the threshold for the secondary endpoint was assigned a target threshold of 75%.

Table 4: Communication Objectives and Target thresholds – LCS IV

#	Communication Objective	Target Level of Comprehension
Primary Objectives		
1	Wash the mouthpiece daily if used	85%
2	Prime before first use	85%
3	Prime the inhaler again if it is: a. wet; b. dropped; c. not used for 2 days	85%
5	Place finger(s) on center of dose indicator	85%
6	Instructions for removing the canister for cleaning mouthpiece	85%
7	Children under 12 years of age: do not use	85%
8	Do not use more than 8 inhalations in 24 hours	85%
9	See your doctor if you have more than 2 asthma attacks in a week	85%
Secondary Objectives		
1	If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take	75%

Source: The Applicant's study report (API-E004-CL-F4), page 10 of 80.

3.2.3 Statistical Methods

3.2.3.1 Analyses of primary and secondary endpoints

Subjects' demographic characteristics were described with summary descriptive statistics (number of participants, mean, standard deviation, median, minimum and maximum) for continuous variables (age) and frequency distributions for categorical variables (e.g., sex, race and literacy level).

For each communication message, the report provided comprehension rates and 95% confidence intervals (exact Clopper-Pearson method). To satisfy the comprehension standard, the lower bound of the 95% confidence interval should exceed the target threshold.

The primary analysis was performed for all participants reviewing the package insert, by literacy level, Primatene® Mist use history, and by asthma status.

The nine primary endpoints were co-primary endpoints, i.e., all the nine endpoints were required to meet the 85% target threshold, therefore there was no need to adjust for multiplicity.

3.2.3.2 Subgroup analyses

Subgroup analyses of comprehension rates included the following subgroups: literacy level, Primatene® Mist use history, and asthma status. In addition to reproducing the sponsor's analyses, the reviewer conducted Fisher's Exact test and Mantel-Haenszel test to compare the findings between the subgroups. Note that confidence intervals of comprehension rates in subgroups will be generally wider confidence than in the general population because subgroups have smaller sample sizes.

3.2.4 Patient Disposition and Demographic Characteristics

A total of 529 participants were qualified for the study at seven sites around the US, 8 participants discontinued the interview prior to beginning the comprehension questions, and 15 participants did not proceed to take the REALM Test. In the end, a total of 504 participants completed the entire interview with the REALM Test.

Within this sample, the mean age was 36.9 (standard deviation was 17.1) and 8.3% of the participants were <18 years of age. Slightly less than half of the sample (45.6%) was male. Participants were reasonably well distributed across race categories; 55.1% were White, 21.9% Black or African American and 14.4% Hispanic or Latino. For education, 13.2% of participants reported that they did not complete their high school education, 27.7% were high school graduates, 35.6% had some college experience, and 23.5% were college graduates. 126 participants (25.0%) were considered low literacy determined by the REALM Test or REALM Teen Test. Approximately 13.8% of the sample reported suffering from asthma. The Primatene® Mist User cohort included only 36 participants (7.1% of the total cohort). The demographic characteristics are listed in Table 5.

Table 5: Demographic characteristics – LCS IV

Characteristics	
N	506
Age	
Mean (Std Dev)	36.9(17.1)
<18 years old, n(%)	42(8.3%)
Sex	
Male, n(%)	230(45.6%)
Race, n(%)	

Characteristics	
White	279(55.1%)
African America	111(21.9%)
Hispanic or Latino	73(14.4%)
Other	43(8.5%)
Education, n(%)	
Did not complete high school	67(13.2%)
High school	140(27.7%)
Some college experience	180(35.6%)
College degree or higher	119(23.5%)
Low literacy, n(%)	126 (25.0%)
Had asthma, n(%)	70(13.8%)
Ever use Primist, n(%)	36(7.1%)

Source: The reviewer's table.

3.2.5 Results

3.2.5.1 Primary analyses

As shown in Table 6, subjects demonstrated high comprehension rate on each of the primary endpoints. The lower bound of the 95% confidence interval for each comprehension rate exceeded the Applicant specified threshold of 85%, with the exception of #3, Prime the inhaler again if it is wet, dropped, or not used for 2 days, where the lower bound of the CI was below the 85% threshold .

Table 6: Results for the primary endpoints – LCS IV

Primary Endpoints	Question # and Text	Comprehension Level (95% CI) N=506
1.Wash the mouthpiece daily if used	**#6: According to the package insert, how often should the mouthpiece be washed?**	95% (93%, 97%)
3. Prime the inhaler again if it is wet, dropped, or not used for 2 days	**#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?**	88% (85%, 90%)
	#4: You must prime the inhaler before you first use it. When else do you have to prime the inhaler again?	83% (79%, 86%)
4. Place finger(s) on center of dose indicator	**#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?**	89% (86%, 92%)
5. Instructions for removing the canister for cleaning mouthpiece	**#7: Susie needs to wash her inhaler. What is the first step she must take?**	96% (93%, 97%)
6. Children under 12 years of age: do not use	**#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?**	97% (95%, 98%)
7. Do not use more than 8 inhalations in 24 hours	**#2: Bill has taken 8 inhalations of (b) (4) today, but is still having asthma symptoms. Is it okay for him to use more Primatene® today?**	92% (89%, 94%)
8. See your doctor if you have more than 2 asthma attacks in a week	**#3: Camille has had 4 asthma attacks in one week. According to the insert, what should Camille do?**	98% (96%, 99%)

*#2 objective, "Prime before first use" was originally planned, but never tested out in LCS IV. It was included in LCS V later.

Source: The reviewer's table. Similar results were also provided in the Applicant's report(API-E004-CL-F4), page 23 of 80.

Reviewer's comments: The primary endpoint #2 "Prime before first use" was not evaluated in this study.

3.2.5.2 Secondary Analyses

As shown in Table 7, comprehension rate was high for the secondary endpoint. The lower bound of the 95% confidence interval for each exceeded the Applicant specified threshold of 85%.

Table 7: Results for the secondary endpoints – LCS IV

Secondary Endpoints	Question # and Text	Comprehension Level (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?**	94% (92%, 96%)

Source: The reviewer's table. Similar results were also provided in the Applicant's report(API-E004-CL-F4), page 24 of 80.

A correct response for this secondary communication objective was a composite of multiple correct responses based on the label tested at the time. However, the current proposed label differs from the label tested in LCS IV. Thus, the reviewer recalculated comprehension for this objective only counting the statements displayed in the current proposed label. The comprehension rates only count those who checked the "Do not rely on dose indicator" and "Keep track of the number of sprays you take" in the questionnaire. The results are in Table 8. There were only 276 (54.6%) participants who checked both options, 77 (15.2%) only checked "Do not rely on dose indicator" and 19 (3.8%) only checked "Keep track of the number of sprays you take".

Table 8: Additional tabulation of Question 9

Question 9	n (%)
Checked "Do not rely on dose indicator" and "Keep track of the number of sprays you take"	276 (54.6%)
Only Checked "Do not rely on dose indicator"	77 (15.2%)
Only Checked "Keep track of the number of sprays you take"	19 (3.8%)
Others	134 (26.5%)

Source: The reviewer's table.

3.2.6 Findings in Subgroup Analyses

This section shows subgroup analyses for each of the primary and secondary endpoints by age, literacy level, experience with product, and asthma history. Below presents the literacy level subgroup analyses, and the Appendix 5.1 includes the results for other subgroup analyses.

3.2.6.1 Literacy Level

The results for literacy level subgroup analyses are in Table 9. Among the 379 participants with normal literacy level, the comprehension rate of each of the primary and secondary communication endpoints were similar to the overall estimates. The lower bound of the 95% confidence interval exceeded the a priori threshold of 85% for all the endpoints. However, the comprehension rates were lower within the 126 low literacy participants compared to the normal literacy group. The lower bound of the 95% confidence interval for the primary endpoints #3, #4, #7 and the secondary endpoint did not exceed the threshold of 85%. The lowest was 56% as for question 4 in the primary endpoint #3.

The reviewer applied Fisher's exact test to compare the comprehension levels between the normal vs and low literacy subgroups. There was significant difference between normal and low literacy groups on almost all the primary and secondary endpoints, except the primary endpoint #5 and #7.

Table 9: Results for literacy subgroup analyses – LCS IV

		Normal Literacy (95% CI) N=379	**Low Literacy (95% CI) N=126**	**p-value**
Primary Endpoints				
1.Wash the mouthpiece daily if used	**#6: According to the package insert, how often should the mouthpiece be washed?**	97% (94%, 98%)	91% (85%, 96%)	0.0265*
2. Prime the inhaler again if it is wet, dropped, or not used for 2 days	**#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%)	0.0074*
	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%)	<0.0001*
3. Place finger(s) on center of dose indicator	**#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%)	0.0289*
4. Instructions for removing the canister for cleaning mouthpiece	**#7: Susie needs to wash her inhaler. What is the first step she must take?**	97% (94%, 98%)	94% (88%, 97%)	0.195

		Normal Literacy (95% CI) N=379	Low Literacy (95% CI) N=126	p-value
5. Children under 12 years of age: do not use	**#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%)	0.0179*
6. Do not use more than 8 inhalations in 24 hours	**#2: Bill has taken 8 inhalations of (b) (4) today, but is still having asthma symptoms. Is it okay for him to use more Primatene® today?**	93% (90%, 95%)	89% (82%, 94%)	0.1863
7. See your doctor if you have more than 2 asthma attacks in a week	**#3: Camille has had 4 asthma attacks in one week. According to the insert, what should Camille do?**	99% (98%, 100%)	95% (90%, 98%)	0.0093*
Secondary Endpoints				
1. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take	**#9: Based on the package insert, what should you do if you drop your inhaler?**	98% (96%, 99%)	85% (77%, 91%)	<0.0001*

Source: The reviewer's table.

* p-values<0.05.

3.3 Label Comprehension Study V

After LCS IV, the package insert was updated to improve communication on priming. The new instructions were tested in LCS V as the Applicant determined that other items were already demonstrated to be understood at an acceptable level in previous comprehension studies for this product. In addition, this study retested an instruction on appropriate finger placement for a puff.

More specifically, the primary objectives of this study were to determine if participants understand the following messages from the package insert:

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; and

4) Place finger(s) on center of dose indicator.

3.3.1 Study Design

This was a multi-center consumer label comprehension study designed to determine the effectiveness of the E004 package insert information. Participants consisted of adults 16 years of age and older selected from the general population at five retail sites across the United States. About 23% of participants were identified as low literacy as defined by the age specific tests of REALM or REALM-Teen. All subjects answered comprehension questions about the proposed package insert.

The Applicant enrolled 492 subjects in this LCS V from five US retail sites as listed below.

- Chicago Ridge Mall, 730 Chicago Ridge Mall, Chicago Ridge, IL. 60415
- Maplewood Mall, 3001 White Bear Ave. N. Space 1070, St. Paul, MN. 55109
- Neshaminy Mall, 109 Neshaminy Mall, Bensalem, PA. 19020
- Roseville Galleria, 1151 Galleria Blvd, Suite 277, Roseville, CA. 95678
- Vancouver Mall, 8700 NE Vancouver Mall Drive, Ste. 187, Vancouver, WA. 98662

3.3.2 Endpoints

Table 10 below lists all communication objectives that were tested in this study along with the corresponding target threshold determined by the Applicant. The thresholds for all the primary endpoints were set at 85%, to keep with previous label comprehension work conducted for E004.

Table 10: Communication Objectives and Target thresholds – LCS V

#	Communication Objective	Target Level of Comprehension
Primary Objectives		
1	Prime before first use	85%
2	Prime the inhaler again if it is wet	85%
3	Prime the inhaler again if it is not used for 2 days	85%
4	Place finger(s) on center of dose indicator	85%

Source: The Applicant's study report (API-E004-CL-F5), page 10 of 76.

3.3.3 Statistical Methods

This study used the same analyses of primary, secondary endpoints and subgroup analyses as the ones in LCS IV and described in Section 3.2.3.

3.3.4 Patient Disposition and Demographic Characteristics

A total of 517 participants were qualified for the study at five sites around the US, 22 participants discontinued the interview prior to beginning the comprehension questions, and 3 participants did not proceed to pass the REALM Test or start the interview. In the end, a total of 492 participants completed the entire interview.

Within this sample, the mean age was 33.5 years (standard deviation was 16.5) and 7.5% of the participants were <18 years of age. Less than half (47.2%) were male. Participants were reasonably well distributed across race categories; 63.4% were White, 20.5% Black or African American and 6.1% Hispanic or Latino. For education, 13.6% of participants reported that they did not complete their high school education, 38.6% were high school graduates, 35.0% had some college experience, and 12.8% were college graduates. 113 participants (23.0%) were considered low literacy determined by the REALM Test or REALM Teen Test. Approximately 17.7% of the sample reported suffering from asthma. The Primatene® Mist User cohort included only 25 participants (5.1% of the total cohort). The demographic characteristics are in Table 11.

Table 11: Demographic characteristics – LCS V

Characteristics	
N	492
Age	
Mean (Std Dev)	33.5(16.5)
<18 years old, n(%)	37(7.5%)
Sex	
Male, n(%)	232(47.2%)
Race, n(%)	
White	312(63.4%)
African America	101(20.5%)
Hispanic or Latino	30(6.1%)
Other	49(10.0%)
Education, n(%)	
Did not complete high school	67(13.6%)
High school	190(38.6%)
Some college experience	172(35.0%)
College degree or higher	63(12.8%)
Low literacy, n(%)	113(23.0%)
Had asthma, n(%)	87(17.7%)
Ever use Primist, n(%)	25(5.1%)

Source: The reviewer's table.

3.3.5 Results

3.3.5.1 Primary analyses

As shown in

Table 12, comprehension rates were high on each of the endpoints. The lower bounds of the 95% confidence intervals for the endpoints of "Prime before first use" and "Place finger on center of dose indicator" exceeded the Applicant threshold of 85%. However, the lower bounds of the 95% confidence intervals for the endpoints of "Prime the inhaler again if it is wet" and "Prime the inhaler again if not used for 2 days" were below the threshold.

Table 12: Results for the primary endpoints – LCS V

Endpoints	Question # and Text	Comprehension Level (95% CI) N=492
1. Prime before first use	**#1: Brenda just purchased (b) (4) What does she need to do to get a new inhaler ready for use?**	88% (85%, 91%)
2. 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?**	91% (88%, 94%)
3. 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?**	86% (82%, 89%)
4. 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?**	83% (79%, 86%)

Source: The reviewer's table. Similar results were also provided in the Applicant's report(API-E004-CL-F5), page 21 of 76.

3.3.6 Subgroup Analyses Results

Subgroup analyses were conducted for each of the primary endpoints within the normal vs low literacy subgroups and also the user vs. non-user subgroups. Below presents the literacy level subgroup analyses, and the Appendix 5.2 includes the results for other subgroup analyses.

3.3.6.1Literacy Level

The results for literacy level subgroup analyses are in Table 13. Comprehension rates were up to 18% lower in the low literacy group (113 participants) compared to the normal literacy group (379 participants). Differences were statistically significant for each of the four comprehension endpoint using Fisher's exact test (type 1 error 5%, two-sided).

Table 13: Results for literacy level subgroup analyses – LCS V

		Normal Literacy (95% CI) N=379	Low Literacy (95% CI) N=113	p-value
Primary Endpoints				
1. 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%)	<0.0001*
2. 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%)	0.0348*
3. 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%)	0.0007*
4. 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%)	<0.0001*

Source: The reviewer's table.

* p-values<0.05.

3.4 Label Comprehension Study VI

The objective of this LCS is to test priming instructions. Some of the priming instructions failed to meet the target comprehension rates in LCS V. Thus, the package insert instructions were modified and the instructions were re-tested in this LCS (LCS VI).

The primary objectives of this study were to determine if participants comprehend the following messages from the package insert:

1) Prime the inhaler again if it is wet; and

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

3.4.1 Study Design

This was a multi-center study. Participants consisted of adults 16 years of age and older selected from the general population at four retail sites across the United States. The study had 20% low literacy participants as determined by the REALM or REALM-Teen. All subjects answered comprehension questions about the proposed package insert.

This Label Comprehension Study (LCS VI) for E004 was conducted at four US retail sites as listed in Table 14.

Table 14: List of study sites-LCS VI

Roseville Galleria	1151 Galleria Blvd, Suite 277	Roseville	CA	95678
Kitsap Mall	10315 Silverdale Way, Suite E20	Silverdale	WA	98383
Citrus Park Mall	7852 Citrus Park Drive	Tampa	FL	33625
Sugarloaf Mills	5900 Sugarloaf Parkway, Suite 125	Lawrenceville	GA	30043

Source: The Applicant's table, page 10 of 63 in the LCS VI study report.

3.4.2 Endpoints

Table 15 below lists all communication objectives that were tested in this study along with the corresponding target threshold. All communication messages were assessed as primary endpoints. The target comprehension thresholds were set at 85% by Applicant, to keep with previous label comprehension work conducted for E004.

Table 15: Communication Objectives and Target thresholds – LCS VI

#	Communication Objective	Target Level of Comprehension
Primary Objectives		
1	Prime the inhaler again if it is wet	85%
2	Prime the inhaler again if it is not used for 2 days	85%

Source: The Applicant's study report (API-E004-CL-F6), page 10 of 63.

3.4.3 Statistical Methods

Statistical methods for primary endpoint and subgroup analyses in this LCS were similar to other two LCS studies as described in Section 3.2.3.

3.4.4 Patient Disposition and Demographic Characteristics

A total of 486 participants were qualified for the study at four sites around the US, 1 participant discontinued the interview prior to beginning the comprehension questions, and a total of 485 participants completed the entire interview.

Within this sample, the mean age was 31.9 (standard deviation was 15.2) and 5.4% of the participants were <18 years of age. A majority of participants (57.1%) were male. Participants were reasonably well distributed across race categories; 55.3% were White, 18.8% Black or African American and 13.0% Hispanic or Latino. For education, 13.6% of participants reported that they did not complete their high school education, 29.3% were high school graduates, 42.3% had some college experience, and 14.8% were college graduates. 98 participants (20.2%) were considered low literacy determined by the REALM Test or REALM Teen Test. Approximately 17.3% of the sample reported suffering from asthma. The Primatene® Mist User cohort included only 31 participants (6.4% of the total cohort). The demographic characteristics were listed in Table 16.

Table 16: Demographic characteristics – LCS VI

Characteristics	
N	485
Age	
Mean (Std Dev)	31.9(15.2)
<18 years old, n(%)	26(5.4%)
Sex	
Male, n(%)	277(57.1%)
Race, n(%)	
White	268(55.3%)
African America	91(18.8%)
Hispanic or Latino	63(13.0%)
Other	63(13.0%)
Education, n(%)	

Characteristics	
Did not complete high school	66(13.6%)
High school	142(29.3%)
Some college experience	205(42.3%)
College degree or higher	72(14.8%)
Low literacy	98 (20.2%)
Had asthma, n(%)	84(17.3%)
Ever use Primist, n(%)	31(6.4%)

Source: The reviewer's table. Similar results were also available in the Applicant's study report (API-E004-CL-F6), page 21 of 63.

3.4.5 Results

3.4.5.1 Primary analyses

As shown in Table 17, subjects demonstrated high comprehension level on both primary endpoints. The lower bound of the 95% confidence interval for each comprehension rate exceeded the Applicant specified threshold of 85%.

Table 17: Results for the primary endpoints – LCS VI

Endpoints	Question # and Text	Comprehension Level (95% CI) N=485
1. Prime the inhaler again if it is wet	**# 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?**	92% (89%, 94%)
4. Prime the inhaler again if it is not used for 2 days	**#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?**	90% (87%, 92%)

Source: The reviewer's table. Similar results were also provided in the Applicant's report(API-E004-CL-F6), page 22 of 63.

3.4.6 Findings in Subgroup Analyses

Subgroup analyses were conducted for each of the primary and secondary endpoints within the normal vs low literacy subgroups and also the user vs. non-user subgroups. The reviewer also conducted subgroup analyses by age. Below presents the literacy level subgroup analyses, and the Appendix 5.3 includes the results for other subgroup analyses.

3.4.6.1 Literacy Level

The results for literacy subgroup analyses are in Table 18. However, the comprehension rates were 7%-8% lower in low literacy group compared to normal literacy group. This is a significant difference based on Fisher's exact test.

Table 18: Results for literacy level subgroup analyses – LCS VI

		Normal Literacy (95% CI) N=387	Low Literacy (95% CI) N=98	p-value
Primary Endpoints				
1. Prime the inhaler again if it is wet	**#1: John cannot let his inhaler dry overnight and must use it when it is 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%)	0.0224*
2. Prime the inhaler again if it is not used for 2 days	**#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%)	0.0006*

Source: The reviewer's table.

* p-values<0.05.

3.5 Human Factor Study

The study objective of this human factor study (G3) was to validate the usability of E004 by following its package insert IFU that is intended to be used in OTC settings. The usability was to characterize

(1) User interface, which consists of the following three tasks:
    (i) Device set-up: assembly;
    (ii) Device use: various aspects, including initial priming/re-priming and routine use; and
    (iii) Device cleaning
(2) Effectiveness;
(3) Efficiency;
(4) Ease of user learning; and
(5) User satisfaction.

3.5.1 Study Design

This study was a Human Factor and Usability Engineering study with 151 participants. The study consisted of approximately 1-hour long, one-on-one sessions with each participant. At the start of the session, study investigators gave participants an opportunity to familiarize themselves with the product. Then, participants were asked to perform a series of tasks with no additional instructions. Finally, participants answered a series of open-ended label comprehension questions.

These Critical Behavioral Tasks (CBTs) are:

(i) Initial priming of the inhaler to prepare it for use;

(ii) Cleaning the inhaler to prevent clogging; and

(iii) Routine use of the inhaler.

Site investigators coded each participant performance in these tasks based on the simulated use portion.

Investigators captured three (3) additional areas of product use and labeling comprehension in an open-ended interview approach using Additional Labeling Human Factor Questions (ALHFQs). The ALHFQs include questions on the following:

(i) How to interpret the dose indicator;

(ii) Not relying on the dose indicator if a device has been dropped; and

(iii) An understanding of the correct finger position required to ensure that the device expels medication properly with each spray.

The study period for this human factors pivotal study G3 for E004 is February to March 2016. This was a multisite study with two study sites listed in Table 19.

Table 19: List of study sites for human factor study (G3)

Site Name	Site Address
HF Labs	8041 Corporate Center Drive Suite 200, Charlotte, NC 28226
Plaza Research	9000 E. Lincoln Drive Building Two Suite 224, Marlton, NJ 08053

Source: The Applicant's table, page 30 of 80 in the HF G3 study report.

3.5.2 Endpoints

The primary and secondary endpoints of Study G3 were defined as follows:

Primary endpoints were the performance scores of the three CBTs, and secondary endpoints were the performance scores of the three ALHFQs.

3.5.3 Statistical Methods

Investigators coded participants' performance for each of the CBTs as completed(C), completed with issues (CI) or not completed(NC);

- Completed (C) — indicates that the participant can successfully perform the use task and demonstrate an understanding of the communication objective.
- Completed with Issues (CI) — indicates that the participant successfully performs the use task and demonstrates an understanding of the communication objective, but either struggles initially to do so, self-corrects during the testing session, or completes the task in such a way that varies from the specific direction provided in the IFU.
- Not Completed (NC) —indicates that the participant does not complete the task successfully and does not demonstrate an understanding of the communication objective.

Participants' performance for each of the ALHFQs were coded and evaluated as correct(C) or Not correct (NC).

- Correct (C) — indicates that the participant, independently and without prompting, can articulate a correct understanding of the communication objective, and can describe the appropriate (i.e., successful) strategy for achieving that objective.
- Not Correct (NC) — indicates that the participant does not articulate a correct understanding of the communication objective, and cannot describe an appropriate (i.e., successful) strategy for achieving that objective.

There were two study populations defined, intent-to-participate population (ITPP) and task evaluable population (TEP). The ITPP of the study is defined as the population of all subjects who was enrolled and was assigned with a participant ID. The TEP is defined as the population of all subjects whose investigator-reported performance score (C, CI, or NC) for all score-coding evaluable sub-items affiliated with this task are available.

The following two (2) datasets with different outcomes codes-were evaluated:

(1) Original Datasets (OD) – all data from the investigator; and

(2) Risk-based Evaluation Data (RBED) – same evaluable population as OD but with outcomes coded as "NC" in OD further assessed based on bench functional test results for E004 inhaler.

Besides the primary and secondary endpoints, the Applicant collected additional data including: Demographic characteristics of participants such as age, gender, race, literacy level (normal or low), participant qualification information, experience with using an MDI inhaler (naïve or experiences); Study basic information such as total time taken by the participant used to read E004 labeling, and whether or not the participant retrieved and reviewed the IFU(Yes/No).

3.5.3.1.1 Analyses of primary endpoint

The acceptable rate (AR) for a given Critical Task-k, denoted as Θ_k (k=1, 2, or 3), is the proportion of subjects who either completed the task correctly (C) or completed with issue (CI) out of all those in the study. More precisely,

$$\theta_k = \frac{N_k(C) + N_k(CI)}{N_k(C) + N_k(CI) + N_k(NC)} \times 100\%$$

Applicant was targeting acceptable rates significantly higher than 85% threshold (5% significance level (2-sided) using clopper-pearson exact method or normal approximation method).

- The primary analysis used RBED;
- For primary analysis, the population will be TEP.

Reviewer's comments: The acceptable rate for a given Critical Task was defined by the review division for this study, Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology, as the proportion of complete response among all the responses. The reviewer calculated the acceptable rate based on DMEPA's definition and performed Binomial tests to check whether AR is greater than the threshold 85%. Clopper-Pearson Exact method was used to construct the 95% confidence intervals.

3.5.3.2 Analyses of secondary endpoints

The AR for a given ALC question-*k*, denoted as Θ_k *(k*=4, 5, or 6), is defined as the proportion of correct responses out of all participants. More precisely,

$$\theta_k = \frac{N_k(C)}{N_k(C) + N_k(NC)} \times 100\%$$

Applicant planned similar statistical analyses for secondary endpoints as that for the primary endpoints.

3.5.3.3 Multiplicity adjustment

The three primary endpoints were co-primary endpoints, i.e., all the three endpoints were required to significantly exceed the 85% target threshold, therefore there was no need to adjust for multiplicity.

3.5.3.4 Subgroup analyses

The subgroup primary and secondary endpoints analyses were performed based on TEP per following categorical variables:

- Age group: Adult vs teen;
- Gender;
- Race;
- Literacy level: normal or low;

- Experience of use MDI inhaler: naïve (never used) or experienced;
- The total time taken by the participant used to read E004 Labeling.

3.5.4 Patient Disposition and Demographic Characteristics

A total of 151 participants enrolled in the study with a participant ID and thus are part of the ITPP. All of the 151 participants had their performance scores available and included in the TEP. So the ITPP population is identical to the TEP population.

The summary of the demographic and related characteristics of participants is in Table 20. There were 151 participants enrolled in this study, including 132 adults (79 women and 72 men) and 19 teens. The mean ages of subjects were 42 years with standard deviation of17 years, with a range of 12 to 78 years of age. The majority of participants were Caucasian (79.5%) with some African American (15.9%) and Hispanic (3%).

Literacy level was assessed by the REALM and REALM TEEN tools. Low literacy level group included 19 adult and 5 teen tested at low literacy level. Thirty-nine (39, 25.8%) participants had prior experience using an inhaler.

Reviewer comment: this review reports different numbers than the Applicant's report for low literacy: "there were 24 (15.9%) adults and 3 juveniles tested at low literacy levels".

Table 20: Demographic and study related information

Populations	Intent-To-Participate Population (ITPP)
# of Subjects	151
Age	
Age (yo), mean ± SD	41.6 ± 16.6
Age (yo), median (range)	42 (12 - 78)
Age Group, n(%)	
Adults	132 (87.4%)
Teens	19 (12.6%)
Gender, n(%)	
Male	72 (47.7%)
Female	79 (52.3%)
Race, n(%)	
Caucasian	120 (79.5%)
African American	24 (15.9%)
Hispanic	5 (3.3%)
Asian	1 (0.7%)
Others	1 (0.7%)
Literacy per REALM	
REALM scores, mean ± SD	63.0 ± 4.9
REALM scores, median (range)	65 (25 - 66)
Literacy Group n(%)▲	
Normal (REALM>60)	126 (83.4%)
Low (REALM≤60)	24 (15.9%)
Experience of Inhaler Usage, n(%)	
Naïve	112 (74.2%)
Experienced	39 (25.8%)
Categories per Multiple Factors, n(%)	
Adults, Naïve, Normal Literacy	86 (57.0%)
Adults, Naïve, Low Literacy	14 (9.3%)
Adults, Experienced, Normal Literacy	27 (17.9%)
Adults, Experienced, Low Literacy	5 (3.3%)
Teens	19 (12.6%)

Source: The Applicant's table, pg 37 of 80 in the HF G3 study report.

▲ One participant (PID=(b) (4) had no REALM score recorded).

3.5.5 Results

The Applicant conducted analyses using the Risk-based evaluation dataset and defined the acceptable rate (for CBTs) as the proportion of Complete and Complete with Issues responses among all the responses. The results from the Applicant's analyses are in Table 21. From the results, all ARs and their lower limits of 95% exact confidence intervals were above 85% for all CBTs/ALHFQs.

Table 21: Primary findings from the human factor study

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).

Source: The Applicant's table, page 4 of 80 in the HF G3 study report.

For comparison purpose, the reviewer conducted additional analyses using both the Risk-based evaluation dataset and the original dataset, using both the applicant's and the DMEPA's definition of acceptable rate. DMEPA defines the CBT acceptable rate as the proportion of only Complete responses among all the responses. The results are listed in Table 22.

By using the original dataset and the Applicant's definition of acceptable rate, the acceptable rate for Task 1 First use was estimated as 91% with 95% confidence intervals as (85%, 95%). By using the DMEPA's definition of acceptable rate for CBTs and only count Complete responses as acceptable, the acceptable rate for Task 1 First use was estimated as 70 % with 95% confidence intervals as (62%, 77%), the acceptable rate for Task 2 Cleaning was estimated as 60% with 95% confidence intervals as (52%, 68%) and the acceptable rate for Task 3 Routine use was estimated as 85% with 95% confidence intervals as (78%, 90%).

The acceptable rates for the three ALHFQ remained the same.

Table 22: Primary analysis results, using both OD and RBED, and using Applicant's and DMEPA's definitions for acceptable rates.

CBT/ALHFQ	Original Dataset (N=151)					Risk-Based Evaluation Dataset (N=151)				
	C	CI	NC	Acceptable Rate by Applicant's definition (95% CI)	Acceptable Rate by DMEPA's definition (95% CI)	C	CI	NC	Acceptable Rate by Applicant's definition (95% CI)	Acceptable Rate by DMEPA's definition (95% CI)
Critical Behavioral Tasks										
Task 1: First Use*	105	**32**	**14**	91% (85%, 95%)	70% (62%, 77%)	105	**38**	**8**	95% (90%, 98%)	70% (62%, 77%)
Task 2: Cleaning	91	56	4	97% (93%, 99%)	60% (52%, 68%)	91	56	4	97% (93%, 99%)	60% (52%, 68%)
Task 3: Routine Use	128	21	2	99% (95%, 100%)	85% (78%, 90%)	128	21	2	99% (95%, 100%)	85% (78%, 90%)
Additional Labeling Human Factor Questions										
Question 4: Dose Indicator	149	--	2	99% (95%, 100%)	99% (95%, 100%)	149	--	2	99% (95%, 100%)	99% (95%, 100%)
Question 5: Dropped Device	147	--	4	97% (93%, 99%)	97% (93%, 99%)	147	--	4	97% (93%, 99%)	97% (93%, 99%)
Question 6: Hold Inhaler Properly	151	--	0	100% (98%, 100%)	100% (98%, 100%)	151	--	0	100% (98%, 100%)	100% (98%, 100%)

Source: The reviewer's table.

*In this study, as opposed to repeatedly shaking and spraying for four times, seven participants shook the inhaler once and sprayed 4 to 5 times consecutively into the air, and six of them completed the priming within 10 seconds. The Applicant argued that the behaviors of these six participants would have no significant impact on user's effective and safe use since the priming were completed within 10 seconds. Thus, these six participants for Task 1 were assigned performance score of Complete with Issues (CI) in the RBE dataset.

3.5.6 Findings in Subgroup Analyses

The subgroup primary and secondary endpoints analyses were performed based on TEP per following categorical variables:

- Age group: Adult vs teen;
- Gender;
- Race;
- Literacy level: normal or low;
- Experience of use MDI inhaler: naïve (never used) or experienced;
- The total time taken by the participant used to read E004 Labeling; and,
- Participant categories.

The following section presents the literacy level subgroup analyses, and the Appendix 5.4 includes the results for other subgroup analyses.

3.5.6.1 Literacy level

The Applicant's results for ARs and their 95% LCI for the two literacy levels (Normal literacy and Low literacy) are summarized in Table 23. For normal literacy subgroup (n=126) subgroup, the ARs and their 95% LCIs for all 6 Tasks/Questions were above 85%. For low literacy subgroup (n=24), the ARs for 5 of 6 Task/Question were higher than 85%; however, the 95% LCIs of ARs for 5 of 6 Tasks/Questions were lower than 85%.

The reviewer applied Fisher's exact test to compare the ARs between the normal vs and low literacy subgroups. There was significant difference between normal and low literacy groups for CBT Task 1, Task 3, ALHFQ Question 4 and Question 5.

Table 23: Subgroup Analysis for CBTs and ALHFQs by Literacy Level

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	>85%?	Exact Method	> 85%?
Normal Literacy								
Task 1 First Use	126	92	30	4	96.8%	√	92.1%	√
Task 2 Cleaning	126	78	46	2	98.4%	√	94.4%	√
Task 3 Routine Use	126	111	15	0	100.0%	√	97.1%	√
Question-4 Dose Indicator	126	126	-	0	100.0%	√	97.1%	√
Question-5 Dropped Device	126	124	-	2	98.4%	√	94.4%	√
Question-6 Hold Inhaler Properly	126	126	-	0	100.0%	√	97.1%	√
All Task/Question-1 to 6					98.9%	√	95.4%	√
Low Literacy								
Task 1 First Use	24	12	8	4	83.3%	x	62.6%	x
Task 2 Cleaning	24	13	9	2	91.7%	√	73.0%	x
Task 3 Routine Use	24	16	6	2	91.7%	√	73.0%	x
Question-4 Dose Indicator	24	22	-	2	91.7%	√	73.0%	x
Question-5 Dropped Device	24	22	-	2	91.7%	√	73.0%	x
Question-6 Hold Inhaler Properly	24	24	-	0	100.0%	√	85.8%	√
All Task/Question-1 to 6					91.7%	√	73.4%	x

Source: The Applicant's table, page 58 of 80 in the HF G3 study report.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

This application includes results from three LCS and one HFS.

Label Comprehension Studies

The three LCS evaluated whether consumers could understand the information on the proposed DFL and PI.

Overall, the three label comprehension studies enrolled more than four hundred subjects, who were 16 years of age or older, from multiple retail sites. The studies used an iterative study design in which initial testing in the first LCS, LCS IV, led to modifications to the DFL and PI. The modified statements were tested in the second LCS, LCS V. In a similar fashion, labeling was refined prior to the start of the sixth LCS, LCS VI, to improve upon any items where consumers did not demonstrate adequate comprehension.

The first label comprehension study LCS IV focused on evaluating instructions for washing, priming, re-priming and using the device. In this study, comprehension rates were significantly higher than 85% for all communication messages, excluding the one for "priming the inhaler when wet or not used for 2 days". The label was revised by Applicant based on the results of LCS IV. Then, the second label comprehension study, LCS V, tested the objective not met in LCS IV, along with other messages on priming. Comprehension rates significantly exceeded 85% for the instruction of "prime before first use and place finger on center of dose indicator" but not "priming

the inhaler when wet or not used for 2 days" Thus, the Applicant further revised the label and re-tested this latter message in LCS VI. This communication objective was finally met in LCS VI with comprehension rate significantly above 85%. Results on all communication objectives in the studies were they were met are in Table 24.

Table 24: Summary Results of Communication Objectives and Rates in LCS IV, LCS V and LCS VI

Communication Objectives	LCS #/Question # and Text	Comprehension Rates (95% CI)
Wash the mouthpiece daily if used	**LCS IV/Q#6: According to the package insert, how often should the mouthpiece be washed?**	95% (93%, 97%)
Place finger(s) on center of dose indicator	**LCS IV/Q#5 and LCS V/Q#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?**	LCS IV 89% (86%, 92%) LCS V 91% (88%, 94%)
Instructions for removing the canister for cleaning mouthpiece	**LCS IV/Q#7: Susie needs to wash her inhaler. What is the first step she must take?**	96% (93%, 97%)
Children under 12 years of age: do not use	**LCS IV/Q#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?**	97% (95%, 98%)
Do not use more than 8 inhalations in 24 hours	**LCS IV/Q#2: Bill has taken 8 inhalations of (b) (4) (b) (4) today, but is still having asthma symptoms. Is it okay for him to use more Primatene® today?**	92% (89%, 94%)
See your doctor if you have more than 2 asthma attacks in a week	**LCS IV/Q#3: Camille has had 4 asthma attacks in one week. According to the insert, what should Camille do?**	98% (96%, 99%)
Prime before first use	**LCS V/Q#1: Brenda just purchased (b) (4) What does she need to do to get a new inhaler ready for use?**	88% (85%, 91%)
Prime the inhaler again if it is wet	**LCS VI/Q# 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?**	92% (89%, 94%)
Prime the inhaler again if it is not used for 2 days	**LCS VI/ Q#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?**	90% (87%, 92%)

Source: The reviewer's Table from individual study results reported in Table 6, Table 12 and Table 17 of this review.

The subgroup analyses in the LCS studies found the following: 1. Age, inhaler use experience and asthma history did not greatly impact comprehension rate; 2. Health literacy impacted comprehension. Comprehension rates were lower for subjects with lower health literacy, prior inhaler experience or asthma history.

The lower bound of 95% confidence intervals for the comprehension level still fell below the 85% threshold in low literacy subjects for the following evaluation objectives:

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

Human Factor Study

After the Applicant determined that the label comprehension studies showed an adequate consumer understanding of the labeling, the Applicant conducted a consumer behavior human factor study. In the human factor study, subjects were instructed to actually demonstrate how to use the product, based upon the labeling. The Applicant carried out the study as a combination of behavioral, simulated use and label comprehension study. During the study, participants were asked to perform all the CBTs (1. Initial Priming; 2. Cleaning to prevent clogging; and 3. Routine use.) required for proper use of the product, and to answer ALHFQs exploring safe use of E004 and supporting labeling (4. How to interpret the dose indicator, 5. Not relying on the dose indicator if a device has been dropped and 6. Understanding the correct finger position when use).

By using the original dataset and the Applicant's definition of acceptable rate, all acceptable rates and their lower limits of 95% exact CI were above 85% for all CBTs/ALHFQs. This definition included not only performances coded as completed but also performances codes as completed with issues. By using the DMEPA's definition of acceptable rate for CBTs and only count Complete responses as acceptable, the acceptable rate for Task 1 First use was estimated as 70 % with 95% confidence intervals as (62%, 77%), the acceptable rate for Task 2 Cleaning was estimated as 60% with 95% confidence intervals as (52%, 68%) and the acceptable rate for Task 3 Routine use was estimated as 85% with 95% confidence intervals as (78%, 90%).

The subgroup analyses found the following 1. Demographic characteristics of age, gender and race did not impact comprehension; and 2. (i) a reading time of E004 IFU, (ii) literacy level, and (iii) prior inhaler experience impacted comprehension rates with lower comprehension rates for subgroup with short reading time, low literacy level or prior inhaler experience.

The comprehension objectives on "Prime the inhaler again if it is wet" and "Prime the inhaler again if not used in 2 days" were tested in all three Label comprehension studies. The thresholds of 85% comprehension level for these objectives were not met in LCS IV, LCS V but were met in LCS VI. Thus, based on the label comprehension studies, this is a challenging instruction for potential users to comprehend in the DFL and PI. However, instructions on using the inhaler if wet or not used in 2 days is not explained well in the proposed IFU ((see Appendices 5.7 and 5.8))

tested in the HFS. The reviewer believes that the additional instructions should be included in the final IFU so that the potential consumers can safely use the product.

4.2 Conclusions and Recommendations

The reviewer was able to reproduce the results provided by the Applicant. Subjects met the performance threshold of 85%, proposed by the Applicant for all the tasks related to priming, cleaning and routine use and all the label comprehension questions on dose indicator, dropped device and holding inhaler properly. The instructions on "Prime the inhaler again if it is wet or not used in 2 days" is an important information for correct use and should be added to the proposed IFU.

It is worth noting that the artificial nature of testing environment may have influenced the performance of subjects in the human factor study. The lack of data from an actual use study gives us no way to determine the consumer's performance in a less artificial setting.

5 APPENDICES

5.1 Additional Subgroup Analyses Results in Label Comprehension Study IV

5.1.1 Age

The results for age subgroup analyses, using categories suggested by Barbara, are in Table 25.

The reviewer applied Mantel-Haenszel test to compare the comprehension levels between the four age subgroups. There was no significant difference between different age groups for the primary endpoints #5, #6 but not for the others.

Table 25: Results for age subgroup analyses – LCS IV

		Age 16-17 (95% CI) N=42	Age18-25 (95% CI) N=147	Age 26-55 (95% CI) N=231	Age 55+ (95% CI) N=86	p-value
Primary Endpoints						
1.Wash the mouthpiece daily if used	**#6: According to the package insert, how often should the mouthpiece be washed?**	95% (84%, 99%)	95% (90%, 98%)	96% (92%, 98%)	94% (87%, 98%)	0.9682
3 Prime the inhaler again if it is wet, dropped, or not used for 2 days	**#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?**	93% (81%, 99%)	91% (85%, 95%)	85% (80%, 90%)	87% (78%, 93%)	0.1589
	Question 4: You must prime the inhaler before you first use it. When else do you have to prime the inhaler again?	71% (55%, 84%)	87% (81%, 92%)	83% (77%, 87%)	80% (70%, 88%)	0.9134
4. Place finger(s) on center of dose indicator	**#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?**	90% (77%, 97%)	90% (85%, 95%)	91% (86%, 94%)	83% (73%, 90%)	0.1481
5. Instructions for removing the canister for cleaning mouthpiece	**#7: Susie needs to wash her inhaler. What is the first step she must take?**	98% (87%, 100%)	99% (95%, 100%)	95% (91%, 97%)	92% (84%, 97%)	0.0162*
6. Children under 12 years of age: do not use	**#1: Meghan has a 6-year old son who has asthma. What, if anything, does the insert say about giving this medicine to her**	93% (81%,	96% (91%,	97% (93%,	100% (96%, 100%)	0.0371*

		Age 16-17 (95% CI) N=42	Age18-25 (95% CI) N=147	Age 26-55 (95% CI) N=231	Age 55+ (95% CI) N=86	p-value
	son?	99%)	98%)	98%)		
7. Do not use more than 8 inhalations in 24 hours	**#2: Bill has taken 8 inhalations of (b) (4) today, but is still having asthma symptoms. Is it okay for him to use more Primatene® today?**	90% (77%, 97%)	93% (87%, 96%)	92% (87%, 95%)	91% (82%, 96%)	0.8432
8. See your doctor if you have more than 2 asthma attacks in a week	**#3: Camille has had 4 asthma attacks in one week. According to the insert, what should Camille do?**	98% (87%, 100%)	99% (96%, 100%)	98% (95%, 99%)	97% (90%, 99%)	0.2780
Secondary Endpoints						
1. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take	**#9: Based on the package insert, what should you do if you drop your inhaler?**	90% (77%, 97%)	96% (91%, 98%)	94% (90%, 96%)	97% (90%, 99%)	0.4928

Source: The reviewer's table.

* p-values<0.05.

5.1.2 Experience with Primist

The results for Primist use subgroup analyses are in Table 26.The comprehension rate for each of the primary and secondary communication endpoints were up to 7% lower in the small Primist user subgroup (36 participant) compared to the large non-user subgroup (469 participants). Nevertheless, none of these differences were statistically significant using Fisher's exact test,

Table 26: Results for Primist use subgroup analyses – LCS IV

		Users (95% CI) N=36	Non-Users (95%CI) N=469	p-value
Primary Endpoints				
1.Wash the mouthpiece daily if used	**#6: According to the package insert, how often should the mouthpiece be washed?**	94% (81%, 99%)	95 % (93%, 97%)	0.6963
3 Prime the inhaler again if it is wet, dropped, or not used for 2 days	**#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?**	81% (64%, 92%)	88% (85%, 91%)	0.1857
	Question 4: You must prime the inhaler before you first use it. When else do you have to prime the inhaler again?	78% (61%, 90%)	83% (79%, 86%)	0.4922
4. Place finger(s) on center of dose indicator	**#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?**	94% (81%, 99%)	89% (86%, 92%)	0.4086
5. Instructions for removing the canister for cleaning mouthpiece	**#7: Susie needs to wash her inhaler. What is the first step she must take?**	100% (90%, 100%)	95% (93%, 97%)	0.3907
6. Children under 12 years of age: do not use	**#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?**	94% (81%, 99%)	97% (95%, 98%)	0.3453
7. Do not use more than 8 inhalations in 24 hours	**#2: Bill has taken 8 inhalations of (b) (4) today, but is still having asthma symptoms. Is it okay for him to use more Primatene® today?**	94% (81%, 99%)	91% (89%, 94%)	0.7573

		Users (95% CI) N=36	Non-Users (95%CI) N=469	p-value
8. See your doctor if you have more than 2 asthma attacks in a week	**#3: Camille has had 4 asthma attacks in one week. According to the insert, what should Camille do?**	100% (90%, 100%)	98% (96%, 99%)	1.0000
Secondary Endpoints				
1. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take	**#9: Based on the package insert, what should you do if you drop your inhaler?**	94% (81%, 99%)	94% (92%, 96%)	1.0000

Source: The reviewer's table.

* p-values<0.05.

5.1.3 History of asthma

The results for asthma history subgroup analyses are in Table 27. The comprehension rates for each of the primary and secondary communication endpoints were up to 7% lower among asthma sufferers (70 participants) compared to the non-asthma sufferers subgroup (436 subgroup). Nevertheless, none of these differences was statistically significant (Fisher's exact test).

Table 27: Results for asthma history subgroup analyses – LCS IV

		Asthma Suffers (95% CI) N=70	Non-Asthma Suffers (95%CI) N=436	p-value
Primary Endpoints				
1.Wash the mouthpiece daily if used	**#6: According to the package insert, how often should the mouthpiece be washed?**	94% (86%, 98%)	95% (93%, 97%)	0.7651
3 Prime the inhaler again if it is wet, dropped, or not used for 2 days	**#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?**	84% (74%, 92%)	88% (85%, 91%)	0.3297
	#4: You must prime the inhaler before you first use it. When else do you have to prime the inhaler	80% (69%, 89%)	83% (79%, 86%)	0.5017

		Asthma Suffers (95% CI) N=70	Non-Asthma Suffers (95%CI) N=436	p-value
	again?			
4. Place finger(s) on center of dose indicator	**#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?**	83% (72%, 91%)	90% (87%, 93%)	0.0918
5. Instructions for removing the canister for cleaning mouthpiece	**#7: Susie needs to wash her inhaler. What is the first step she must take?**	96% (88%, 99%)	96% (93%, 97%)	1.0000
6. Children under 12 years of age: do not use	**#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?**	97% (90%, 100%)	97% (94%, 98%)	1.0000
7. Do not use more than 8 inhalations in 24 hours	**#2: Bill has taken 8 inhalations of (b) (4) today, but is still having asthma symptoms. Is it okay for him to use more Primatene® today?**	86% (75%, 93%)	93% (90%, 95%)	0.0612
8. See your doctor if you have more than 2 asthma attacks in a week	**#3: Camille has had 4 asthma attacks in one week. According to the insert, what should Camille do?**	97% (90%, 100%)	98% (96%, 99%)	0.6355
Secondary Endpoints				
1. If you drop your inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take	**#9: Based on the package insert, what should you do if you drop your inhaler?**	93% (84%, 98%)	95% (92%, 97%)	0.5703

Source: The reviewer's table.

* p-values<0.05.

5.2 Additional Subgroup Analyses Results in Label Comprehension Study V

5.2.1 Age

The results for age subgroup analyses are in Table 28.

The reviewer applied Mantel-Haenszel test to compare the comprehension levels between the four age subgroups. There was no significant difference between different age groups for all the primary endpoints.

Table 28: Results for age subgroup analyses – LCS V

		Age 16-17 (95% CI) N=37	Age18-25 (95% CI) N=196	Age 26-55 (95% CI) N=190	Age 55+ (95% CI) N=69	p-value
Primary Endpoints						
1. Prime before first use	**1. Prime before first use**	89% (75%, 97%)	90% (85%, 94%)	85% (79%, 90%)	91% (82%, 97%)	0.7728
2. Place finger on center of dose indicator	**2. Place finger on center of dose indicator**	89% (75%, 97%)	94% (90%, 97%)	91% (85%, 94%)	87% (77%, 94%)	0.2016
3. Prime the inhaler again if it is wet	**3. Prime the inhaler again if it is wet**	95% (81%, 99%)	86% (81%, 91%)	84% (78%, 89%)	83% (72%, 91%)	0.1179
4. Prime the inhaler again if it is not used for 2 days	**4. Prime the inhaler again if it is not used for 2 days**	84% (68%, 94%)	85% (79%, 90%)	82% (76%, 87%)	80% (68%, 88%)	0.3565

Source: The reviewer's table.

* p-values<0.05.

5.2.2 Experience with Primist

The results for literacy level subgroup analyses are in Table 29. Comprehension rates were up to 13% lower in the previous experience of using Primist group (25 participants) compared to non-user group (467 participants).

However, none of the differences was statistically significant using Fisher's exact test.

Table 29: Results for Primist use subgroup analyses – LCS V

		Users (95% CI) N=25	Non-Users (95%CI) N=467	p-value
Primary Endpoints				
1. Prime before first use	**#1: Brenda just purchased [redacted](b) (4) What does she need to do to get a new inhaler ready for use?**	76% (55%, 91%)	89% (86%, 92%)	0.101
2. 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?**	80% (59%, 93%)	92% (89%, 94%)	0.057
3. 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?**	76% (55%, 91%)	86% (83%, 89%)	0.2356
4. 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?**	80% (59%, 93%)	83% (79%, 86%)	0.5964

Source: The reviewer's table.

* p-values<0.05.

5.2.3 History of asthma

The results for asthma history subgroup analyses are in Table 30. The comprehension rates were up to 8% lower in asthma sufferers compared to the non-asthma sufferers group.

However, only comprehension rates of endpoint #2 were statistically significant between the two groups.

Table 30: Results for asthma history subgroup analyses – LCS V

	Asthma Suffers (95% CI) N=87	Non-Asthma Suffers (95%CI) N=405	p-value

		Asthma Suffers (95% CI) N=87	Non-Asthma Suffers (95%CI) N=405	p-value
Primary Endpoints				
1. Prime before first use	**#1: Brenda just purchased [redacted] (b) (4) What does she need to do to get a new inhaler ready for use?**	84% (74%, 91%)	89% (86%, 92%)	0.1982
2. 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?**	85% (76%, 92%)	93% (90%, 95%)	0.0345*
3. 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?**	79% (69%, 87%)	87% (83%, 90%)	0.0909
4. 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?**	84% (74%, 91%)	83% (79%, 86%)	0.876

Source: The reviewer's table.

* p-values<0.05.

5.3 Additional Subgroup Analyses Results in Label Comprehension Study VI

5.3.1 Age

The results for age subgroup analyses are in Table 31.

The Mantel-Haenszel shows no significant difference between different age groups for all the primary endpoints.

Table 31: Results for age subgroup analyses – LCS VI

		Age 16-17 (95% CI) N=26	Age18-25 (95% CI) N=214	Age 26-55 (95% CI) N=193	Age 55+ (95% CI) N=52	p-value
Primary Endpoints						
1. Prime the inhaler again if it is wet	**#1: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do if he needs to use it when it is still wet?**	92% (75%, 99%)	92% (87%, 95%)	93% (89%, 96%)	87% (74%, 94%)	0.5622
2. Prime the inhaler again if it is not used for 2 days	**#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?**	81% (61%, 93%)	89% (84%, 93%)	92% (87%, 95%)	88% (77%, 96%)	0.3284

Source: The reviewer's table.

* p-values<0.05.

5.3.2 Experience with Primist use

The results for Primist use experience are in Table 32. Comprehension rates were lower (by 2% for one question and 6% in another question) for Primist users (31 participants) compared to non-user group (454 participants).

This difference was not statistically significant (Fisher's exact test)

Table 32: Results for Primist use subgroup analyses – LCS VI

		Users (95% CI) N=31	**Non-Users (95%CI) N=454**	**p-value**
Primary Endpoints				
1. Prime the inhaler again if it is wet	**#1: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do if he needs to use it when it is still wet?**	90% (74%, 98%)	92% (89%, 94%)	0.7337
2. Prime the inhaler again if it is not used for 2 days	**#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?**	84% (66%, 95%)	90% (87%, 93%)	0.3523

Source: The reviewer's table.

* p-values<0.05.

5.3.3 History of asthma

The results for the asthma history subgroup analyses are in **Table 33**. The comprehension levels for each of the primary communication endpoints among asthma suffers were similar to the non-asthma suffers group (within 1%).

Table 33: Results for asthma history subgroup analyses – LCS VI

		Asthma Suffers (95% CI) N=84	Non-Asthma Suffers (95%CI) N=401	p-value
Primary Endpoints				
1. Prime the inhaler again if it is wet	**#1: John cannot let his inhaler dry overnight and must use it when it is wet. What does the package insert say John should do if he needs to use it when it is still wet?**	93% (85%, 97%)	92% (88%, 94%)	0.8289
2. Prime the inhaler again if it is not used for 2 days	**#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?**	89% (81%, 95%)	90% (86%, 93%)	0.8452

Source: The reviewer's table.

* p-values<0.05.

5.4 Additional Subgroup Analyses Results in Human Factor Study G3

5.4.1 Age

The results for ARs and their 95% LCI for the two age groups (Adult and Teen) are summarized in Table 34.

Table 34: Subgroup Analysis for CBTs and ALHFQs by Age Groups – HF study

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	>85%?	Exact Method	>85%?
Adults								
Task 1 First Use	132	91	34	7	94.7%	√	89.4%	√
Task 2 Cleaning	132	81	49	2	98.5%	√	94.6%	√
Task 3 Routine Use	132	110	21	1	99.2%	√	95.9%	√
Question-4 Dose Indicator	132	130	-	2	98.5%	√	94.6%	√
Question-5 Dropped Device	132	128	-	4	97.0%	√	92.4%	√
Question-6 Hold Inhaler Properly	132	132	-	0	100.0%	√	97.2%	√
All Task/Question-1 to 6					98.0%	√	94.0%	√
Teens								
Task 1 First Use	19	14	4	1	94.7%	√	74.0%	x
Task 2 Cleaning	19	10	7	2	89.5%	√	66.9%	x
Task 3 Routine Use	19	18	0	1	94.7%	√	74.0%	x
Question-4 Dose Indicator	19	19	-	0	100.0%	√	82.4%	x
Question-5 Dropped Device	19	19	-	0	100.0%	√	82.4%	x
Question-6 Hold Inhaler Properly	19	19	-	0	100.0%	√	82.4%	x
All Task/Question-1 to 6					96.5%	√	77.0%	x

Source: The Applicant's table, page 54 of 80 in the HF G3 study report.

5.4.2 Gender

The results for ARs and their 95% LCI for the gender groups were summarized in Table 35. The ARs and their 95% LCIs for 5 of 6 Tasks/Questions in male subgroup were above 85%, except the LCI for Task-1 was 79.3%. The ARs and their 95% LCIs for all 6 Tasks/Questions in female subgroup were above 85%.

Table 35: Subgroup Analysis for CBTs and ALHFQs by Gender – HF study

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	>85%?	Exact Method	>85%?
Males								
Task 1 First Use	72	43	21	8	88.9%	√	79.3%	x
Task 2 Cleaning	72	42	27	3	95.8%	√	88.3%	√
Task 3 Routine Use	72	60	11	1	98.6%	√	92.5%	√
Question-4 Dose Indicator	72	70	-	2	97.2%	√	90.3%	√
Question-5 Dropped Device	72	69	-	3	95.8%	√	88.3%	√
Question-6 Hold Inhaler Properly	72	72	-	0	100.0%	√	95.0%	√
All Task/Question-1 to 6					96.1%	√	89.0%	√
Females								
Task 1 First Use	79	62	17	0	100.0%	√	95.4%	√
Task 2 Cleaning	79	49	29	1	98.7%	√	93.2%	√
Task 3 Routine Use	79	68	10	1	98.7%	√	93.2%	√
Question-4 Dose Indicator	79	79	-	0	100.0%	√	95.4%	√
Question-5 Dropped Device	79	78	-	1	98.7%	√	93.2%	√
Question-6 Hold Inhaler Properly	79	79	-	0	100.0%	√	95.4%	√
All Task/Question-1 to 6					99.4%	√	94.3%	√

Source: the Applicant's table, page 55 of 80 in the HF G3 study report.

5.4.3 Race

The results for ARs and their 95% LCI for the three race groups (White, African-America and Others) were summarized in Table 36. For white (Caucasian, n=120) subgroup, the ARs and their 95% LCIs for all 6 Tasks/Questions were above 85%. For African-American (n=24) subgroup The ARs for 5 of 6 Task/Question were higher than 85%; however, the 95% LCIs of ARs for 5 of 6 Tasks/Questions were lower than 85%. For other race subgroup (n=7), the ARs were higher than 85%; however, the 95% LCIs of ARs were lower than 85% due to the small sample size.

Table 36: Subgroup Analysis for CBTs and ALHFQs by Race – HF study

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	>85%?	Exact Method	>85%?
White (Caucasian)								
Task 1 First Use	120	88	29	3	97.5%	√	92.9%	√
Task 2 Cleaning	120	70	47	3	97.5%	√	92.9%	√
Task 3 Routine Use	120	105	15	0	100.0%	√	97.0%	√
Question-4 Dose Indicator	120	120	-	0	100.0%	√	97.0%	√
Question-5 Dropped Device	120	118	-	2	98.3%	√	94.1%	√
Question-6 Hold Inhaler Properly	120	120	-	0	100.0%	√	97.0%	√
All Task/Question-1 to 6					98.9%	√	95.1%	√
African-American								
Task 1 First Use	24	13	6	5	79.2%	x	57.9%	x
Task 2 Cleaning	24	15	8	1	95.8%	√	78.9%	x
Task 3 Routine Use	24	17	5	2	91.7%	√	73.0%	x
Question-4 Dose Indicator	24	22	-	2	91.7%	√	73.0%	x
Question-5 Dropped Device	24	22	-	2	91.7%	√	73.0%	x
Question-6 Hold Inhaler Properly	24	24	-	0	100.0%	√	85.8%	√
All Task/Question-1 to 6					91.7%	√	73.6%	x
Others								
Task 1 First Use	7	4	3	0	100.0%	√	59.0%	x
Task 2 Cleaning	7	6	1	0	100.0%	√	59.0%	x
Task 3 Routine Use	7	6	1	0	100.0%	√	59.0%	x
Question-4 Dose Indicator	7	7	-	0	100.0%	√	59.0%	x
Question-5 Dropped Device	7	7	-	0	100.0%	√	59.0%	x
Question-6 Hold Inhaler Properly	7	7	-	0	100.0%	√	59.0%	x
All Task/Question-1 to 6					100.0%	√	59.0%	x

Source: The Applicant's table, page 56 of 80 in the HF G3 study report.

5.4.4 Experience of use MDI inhaler

The results for ARs and their 95% LCI for the prior inhaler experience (Naïve and Experienced) were summarized in Table 37. For inhaler naïve subgroup (n=112), the ARs and their 95% LCIs for all 6 Tasks/Questions were above 85%. For experienced subgroup (n=39), the ARs for all 6 Task/Question were higher than 85%; however, the 95% LCIs of ARs for 4 of 6 Tasks/Questions were lower than 85%.

Table 37: Subgroup Analysis for CBTs and ALHFQs by Prior Inhaler Experience – HF study

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	> 85%?	Exact Method	> 85%?
Inhaler Naïve								
Task 1 First Use	112	80	29	3	97.3%	√	92.4%	√
Task 2 Cleaning	112	65	45	2	98.2%	√	93.7%	√
Task 3 Routine Use	112	96	15	1	99.1%	√	95.1%	√
Question-4 Dose Indicator	112	112	-	0	100.0%	√	96.8%	√
Question-5 Dropped Device	112	111	-	1	99.1%	√	95.1%	√
Question-6 Hold Inhaler Properly	112	112	-	0	100.0%	√	96.8%	√
All Task/Question-1 to 6					99.0%	√	95.0%	√
Experienced								
Task 1 First Use	39	25	9	5	87.2%	√	72.6%	x
Task 2 Cleaning	39	26	11	2	94.9%	√	82.7%	x
Task 3 Routine Use	39	32	6	1	97.4%	√	86.5%	√
Question-4 Dose Indicator	39	37	-	2	94.9%	√	82.7%	x
Question-5 Dropped Device	39	36	-	3	92.3%	√	79.1%	x
Question-6 Hold Inhaler Properly	39	39	-	0	100.0%	√	91.0%	√
All Task/Question-1 to 6					94.4%	√	82.4%	x

Source: The Applicant's table, page 59 of 80 in the HF G3 study report.

5.4.5 The total time taken by the participant used to read E004 IFU

The results for ARs and their 95% LCI for the two labelling reading time categories (≥1 minute and <1 minute) were summarized in Table 38. For the subgroup who spent 1 minute or more (n=145), the ARs and their 95% LCIs for all 6 Tasks/Questions were above 85%. For the subgroup who spent less than 1 minute (n=6), the ARs and 3 of 6 Tasks or Questions were less 85%.

Table 38: Subgroup Analysis for CBTs and ALHFQs by IFU Reading Time – HF study

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	> 85%?	Exact Method	> 85%?
Total Reading Time ≥ 1 minute								
Task 1 First Use	145	104	36	5	96.6%	√	92.1%	√
Task 2 Cleaning	145	90	51	4	97.2%	√	93.1%	√
Task 3 Routine Use	145	122	21	2	98.6%	√	95.1%	√
Question-4 Dose Indicator	145	144	-	1	99.3%	√	96.2%	√
Question-5 Dropped Device	145	142	-	3	97.9%	√	94.1%	√
Question-6 Hold Inhaler Properly	145	145	-	0	100.0%	√	97.5%	√
All Task/Question-1 to 6					98.3%	√	94.7%	√
Total Reading Time: < 1 minute								
Task 1 First Use	6	1	2	3	50.0%	x	11.8%	x
Task 2 Cleaning	6	1	5	0	100.0%	√	54.1%	x
Task 3 Routine Use	6	6	0	0	100.0%	√	54.1%	x
Question-4 Dose Indicator	6	5	-	1	83.3%	x	35.9%	x
Question-5 Dropped Device	6	5	-	1	83.3%	x	35.9%	x
Question-6 Hold Inhaler Properly	6	6	-	0	100.0%	√	54.1%	x
All Task/Question-1 to 6					86.1%	√	41.0%	x

Source: The Applicant's table, page 61 of 80 in the HF G3 study report.

5.4.6 Participant Categories

The results for ARs and their 95% LCI for the 5 participant categories (Adult, naïve and normal literacy; Adult, experienced and normal literacy; Adult, naïve and low literacy; Adult, experienced and low literacy; and Teen) were summarized in Table 39.

For the "Adults, naïve, normal literacy" subgroup (n=86), the ARs and their 95% LCIs for all 6 Tasks/Questions were above 85%. For the "Adults, experienced, normal literacy" subgroup (n=27), the ARs for all 6 Tasks/Questions were above 85%, and 3 of 6 LCI for ARs were lower than 85%. For the "Adults, naive, low literacy" subgroup (n=14), the ARs for all 6 Tasks/Questions were above 85%, and all of 6 LCI for ARs were lower than 85%. For the "Adults, experienced, low literacy" subgroup (n=5), the ARs for 2 of 6 Tasks/Questions were above 85%, and all of 6 LCI for ARs were lower than 85%. For "teens" subgroup (n=19), the ARs for all 6 Tasks/Questions were above 85%, but none of the 6 LCI for ARs were above 85%.

Table 39: Subgroup Analysis for CBTs and ALHFQs by Multiple Factors – HF study

CBT/ALHFQ	# of Participants (TEP*)	Global Results					Lower Limit of 95% confidence Interval, %	
		C	CI	NC	Acceptable Rate			
					%	> 85%?	Exact Method	> 85%?
Adults, Naive, Normal Literacy								
Task 1 First Use	86	63	22	1	98.8%	√	93.7%	√
Task 2 Cleaning	86	49	37	0	100.0%	√	95.8%	√
Task 3 Routine Use	86	75	11	0	100.0%	√	95.8%	√
Question-4 Dose Indicator	86	86	-	0	100.0%	√	95.8%	√
Question-5 Dropped Device	86	85	-	1	98.8%	√	93.7%	√
Question-6 Hold Inhaler Properly	86	86	-	0	100.0%	√	95.8%	√
All Task/Question-1 to 6					**99.6%**	√	**95.1%**	√
Adults, Experienced, Normal Literacy								
Task 1 First Use	27	20	5	2	92.6%	√	75.7%	x
Task 2 Cleaning	27	21	5	1	96.3%	√	81.0%	x
Task 3 Routine Use	27	23	4	0	100.0%	√	87.2%	√
Question-4 Dose Indicator	27	27	-	0	100.0%	√	87.2%	√
Question-5 Dropped Device	27	26	-	1	96.3%	√	81.0%	x
Question-6 Hold Inhaler Properly	27	27	-	0	100.0%	√	87.2%	√
All Task/Question-1 to 6					**97.5%**	√	**83.2%**	x
Adults, Naive, Low Literacy								
Task 1 First Use	14	7	5	2	85.7%	√	57.2%	x
Task 2 Cleaning	14	7	6	1	92.9%	√	66.1%	x
Task 3 Routine Use	14	10	4	0	100.0%	√	76.8%	x
Question-4 Dose Indicator	14	14	-	0	100.0%	√	76.8%	x
Question-5 Dropped Device	14	14	-	0	100.0%	√	76.8%	x
Question-6 Hold Inhaler Properly	14	14	-	0	100.0%	√	76.8%	x
All Task/Question-1 to 6					**96.4%**	√	**71.8%**	x
Adults, Experienced, Low Literacy								
Task 1 First Use	5	1	2	2	60.0%	x	14.7%	x
Task 2 Cleaning	5	4	1	1	100.0%	√	47.8%	x
Task 3 Routine Use	5	2	2	1	80.0%	x	28.4%	x
Question-4 Dose Indicator	5	3	-	2	60.0%	x	14.7%	x
Question-5 Dropped Device	5	3	-	2	60.0%	x	14.7%	x
Question-6 Hold Inhaler Properly	5	5	-	0	100.0%	√	47.8%	x
All Task/Question-1 to 6					**76.7%**	x	**28.0%**	x
Teens								
Task 1 First Use	19	14	4	1	94.7%	√	74.0%	x
Task 2 Cleaning	19	10	7	2	89.5%	√	66.9%	x
Task 3 Routine Use	19	18	0	1	94.7%	√	74.0%	x
Question-4 Dose Indicator	19	19	-	0	100.0%	√	82.4%	x
Question-5 Dropped Device	19	19	-	0	100.0%	√	82.4%	x
Question-6 Hold Inhaler Properly	19	19	-	0	100.0%	√	82.4%	x
All Task/Question-1 to 6					**96.5%**	√	**77.0%**	x

Source: The Applicant's table, page 62 of 80 in the HF G3 study report.

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/s/

RIMA IZEM

12/07/2016

The primary statistical reviewer and author of this review is Dr. Yueqin Zhao. Dr. Zhao is not submitting this review because she is on maternity leave. Thus, this review is submitted by Team Leader Rima Izem after completion of the secondary and tertiary reviews.

MARK S LEVENSON

12/07/2016