CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205920Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 205920
Review #3

Drug Name/Dosage Form	Epinephrine Inhalation Aerosol
Strength	125 mcg/actuation
Route of Administration	Oral inhalation
Rx/OTC Dispensed	OTC
Applicant	Armstrong Pharmaceuticals, Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission	5/7/2018	Drug Product, Facilities
Amendments	10/11/2018	Drug Product

Quality Review Team

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

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate		Review in DARRTS 7/15/13
	III			Adequate	Reviewed this cycle 11/15/2016	Reviews in DARRTS 8/11/11 11/15/16
	III			Adequate		Information in the application reviewed during first cycle See CMC review in DARRTS 4/25/2014
	III			Adequate		As above
	III			Adequate		As above
	III			Adequate		As above
	III			Adequate		As above

		(b) (4)			
(b) (4)	III		Adequate		As above
	IV		Adequate		Review in DARRTS 2/15/12
	V		Adequate		See Dr. Harrouk's filing review in DARRTS 9/19/13

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	74286	Epinephrine HFA inhalation aerosol
NDA	16126- withdrawn	Primatene mist
ANDA	87907- withdrawn	Primatene mist

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/ Toxicology	Complete	Approval	11/16/ 2016	D.C. Thompson
CDRH-OC	Complete	Approval	12/1/ 2016 See memo. and adde-ndum in DARRTS	Jamie Kamon-Brancazio

Executive Summary

I. Recommendations and Conclusion on Approvability

Approval from CMC perspective. CMC review concludes that the epinephrine inhalation aerosol is a drug product with similar quality performance as prescription inhalation aerosols (MDIs) containing HFA and that the labeling instructions for use are supported by sufficient CMC characterization data.
Note that the facilities recommendation for this review cycle is pending, but the facilities were deemed acceptable during the previous cycle (see OPQ review in Panorama, dated 12/2/2016).
The drug substance manufacturer, (b) (4) maintains an active DMF (b) (4) with the FDA and has received acceptable cGMP recommendation in 2016 (see OPQ review #2, dated 12/2/2016 in Panorama). The applicant has procured supplies of epinephrine from (b) (4) or manufacture of drug product (b) (4) In addition, the applicant committed to (b) (4) This provides for an acceptable, viable manufacturing supply chain of the drug product. See details in executive summary, below.

Language to include in the Action Letter:

" We acknowledge your submission dated October 11, 2018 which states that you will use epinephrine batches from (b) (4) for production of drug product, and (b) (4) remains your commercial supplier until 2019. In addition, we acknowledge your commitment, to (b) (4)

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	**For temporary relief of mild symptoms of intermittent asthma in adults and children over 12 years of age**
Duration of Treatment	**Intermittent**
Maximum Daily Dose	**8 inhalations over 24 h 1000mcg; 1 mg**
Alternative Methods of Administration	**NA**

B. Quality Assessment Overview

See OPQ review #2, dated 12/2/2016, in Panorama for product background and regulatory history of the application. The OPQ review of 12/2/2016 recommended approval from a quality perspective. NDA 205920 received a CR letter on 12/23/16 and was resubmitted on 5/7/18.

The applicant responded to label comprehension deficiencies in the CR letter issued during the second review cycle, by conducting additional studies supported by CMC characterization data for the drug product.

In the CR Letter of 12/23/16, the applicant was asked to either develop an alternate inhalation device or to optimize labeling of the existing device to improve patient understanding and ability to perform successfully the tasks of priming, cleaning and routine use (re-priming). If these tasks are not successfully performed, the patient will not reliably receive the correct dose and may either under-dose or receive a supra-therapeutic dose. The applicant was asked to repeat and validate the critical tasks of the HF study and include at least 15 users in each distinct user group. Users should include adolescents, low literacy, asthma patients and subjects with previous inhaler experience.

- Initial prime: Four times shake/spray: Dr. Ramaswamy analyzed additional information evaluating the risk to delivered dose content uniformity (DDU). Based on emitted dose data for various samples collected through container shelf-life, the applicant concluded that the risk of receiving an under-dose (<70 % LC) from the inhaler is up to 29% and the risk of receiving a supra-therapeutic dose (>200% LC) is 9%. Failure to shake is critical each time prior to inhaler use. Deviations to initial priming (1 shake/1 spray or 2 shake/2 spray or 3 shake/3 spray or 1 shake/4 spray) or no initial priming or not wasting or discarding the initial first 4 sprays result in under-dose. The applicant concluded that remediation is taking an additional dose.
- Cleaning frequency: Clean each day after use: The applicant performed cleaning studies that resulted in no clogging after 3 days of use and then cleaning as evaluated in CMC reviews #1 and #2. In this submission the applicant performed a study in which inhalers were used without cleaning for 20 days. Results indicated that beyond 7 days of use without cleaning resulted in delivery of inconsistent dose. Beyond the 7 days of use, dose inconsistency is shown by larger standard deviation (after 7 days DDU=103.3±9.2% to 118.9±19.5% versus for 1-7 days 101.4±7.1% - 108.4±8.1%). No data on aerodynamic particle size distribution, % respirable dose and % respirable fraction were provided for the 20-day study. Dr. Ramaswamy concluded that the original instruction "Wash every day if used" is a more conservative instruction and that the most recent study is not sufficient.
- Re-priming: Re-prime before each use: (shake/spray discard): The original study concluded that re-prime after 48h of use was acceptable. Beyond 48 hours storage, the probability that average dose content of the first two sprays will be an under-dose (<70 % LC) is 15.6-17%. The applicant evaluated re-priming in the recent 20-day study. After a resting period of 1-20 days, the 5^{th} spray and 5^{th}+6^{th} spray data corresponding to the various rest periods were analyzed. Study results showed that the 5^{th} spray had a potential to deliver an under-dose after 2 days resting and the 5^{th}+6^{th} spray dispensed an acceptable

dose after 14 days resting (without re-prime). This study discounts previous study results. Dr. Ramaswamy concluded that the original re-prime frequency before each use is a more conservative approach that results in delivery of a consistent and uniform dose.

The conclusion of the drug product review is that the product performs as expected of HFA MDIs and that the labeling instructions for use are supported by sufficient CMC characterization data. The ability of the patients to comprehend and execute these instructions in the OTC setting was discussed with the clinical team and agreement was reached on the conservative labeling instructions supported by CMC data on delivered dose content uniformity (DDU).

With respect to cGMP compliance of manufacturing facilities **see facilities review, 12/2/2016 (Panorama),** previous cycle. A recommendation for the manufacturing facilities for this cycle is pending.

In his 2016 facilities review, Mr. Carl Lee discussed inspection results for the drug substance manufacturer (b) (4) to address GMP deficiencies cited in the CR letter during first cycle review and this facility was deemed acceptable. Armstrong Pharmaceuticals, Inc. (FEI: 3007009553), the drug product manufacturer was inspected during first cycle and is acceptable by profile. The CDRH-OC inspectional memorandum (see DARRTS 12/1/2016) for compliance of the device with device regulations determined that no pre-approval inspection was required as the recent Drug GMP inspection of the firm covered elements that demonstrated compliance of the facility and the device.

- Drug Substance Manufacturer:

New information regarding the status of manufacturing campaigns for epinephrine at (b) (4) came to our attention. The single drug substance manufacturer (b) (4) has ceased manufacture of epinephrine in 12/2017. We discussed this with the applicant during the 10/2/2018 t-con and Armstrong replied that they procured epinephrine supplies (b) (4) manufactured under GMP projected (b) (4) manufacture of drug product and that (b) (4) remains an active epinephrine supplier for this application until 2019. DMF (b) (4) by (b) (4) remains active with the FDA. (b) (4) Armstrong completed 2-year stability studies of drug product manufactured from (b) (4) drug substance. Note that (b) (4) maintains an active and adequate DMF (b) (4) with the FDA which supported recent approvals (NDA (b) (4) and NDA (b) (4)).

On 10/11/2018, Armstrong submitted to NDA 205920 a quality amendment documenting the epinephrine supply by (b) (4)

I conclude that the proposal by Armstrong to continue using (b) (4) drug substance (b) (4) is adequate based on the fact that the procured batches were

manufactured under GMPs and that (b) (4) maintains possession of the epinephrine batches and an active and adequate DMF (b) (4) at the time of action for this NDA. See above, language to include in the Action Letter acknowledging the applicant's commitment for their commercial production of Primatene mist.

C. Special Product Quality Labeling Recommendations (NDA only) communicated to the applicant during a t-con on 10/2/2018:

1. Initial priming: 4 shake/spray
2. Cleaning: Clean after each day of use
3. Re-priming: Shake and spray before each use

D. Final Risk Assessment: See attachment to IQA.

Recommendation: APPROVAL

NDA 205920
Review #2

Drug Name/Dosage Form	Epinephrine Inhalation Aerosol
Strength	125 mcg/actuation
Route of Administration	Oral inhalation
Rx/OTC Dispensed	OTC
Applicant	Armstrong Pharmaceuticals, Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission	6/28/2016	Drug Product, Facilities
Amendments	7/18/2016 7/22/2016 9/6/2016 9/19/2016 10/17/2016	Drug Product Labeling Labeling Labeling Labeling

Quality Review Team

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

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	III			Adequate	Reviewed this cycle 11/15/2016	Reviews in DARRTS 8/11/11 11/15/16
	III			Adequate		Information in the application reviewed during first cycle See CMC review in DARRTS 4/25/2014
	III			Adequate		As above
	III			Adequate		As above
	III			Adequate		As above
	III			Adequate		As above

		(b) (4)			
(b) (4)	III		Adequate		As above
	IV		Adequate		Review in DARRTS 2/15/12
	V		Adequate		See Dr. Harrouk's filing review in DARRTS 9/19/13

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	74286	Epinephrine HFA inhalation aerosol
NDA	16126- withdrawn	Primatene mist
ANDA	87907- withdrawn	Primatene mist

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/ Toxicology	Complete	Approval	11/16/ 2016	D.C. Thompson
CDRH-OC	Pending	Approval	12/1/ 2016 See memo. and addendum in DARRTS	Jamie Kamon-Brancazio

Executive Summary

I. Recommendations and Conclusion on Approvability

Approval from CMC perspective. CMC review concludes that the epinephrine inhalation aerosol is a drug product with similar quality performance as prescription inhalation aerosols (MDIs) containing HFA and that the labeling instructions for use are supported by sufficient CMC characterization data.
The suitability of this product for OTC use is deferred to the clinical team's evaluation.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	**For temporary relief of mild symptoms of intermittent asthma in adults and children over 12 years of age**
Duration of Treatment	**Intermittent**
Maximum Daily Dose	**8 inhalations over 24 h 1000mcg; 1 mg**
Alternative Methods of Administration	**NA**

B. Quality Assessment Overview

NDA 205920 received a CR letter on 5/22/14 and was resubmitted on 6/28/16. The applicant responded to label comprehension deficiencies in the CR letter issued during the first review cycle, by conducting additional studies supported by CMC characterization data for the drug product.
The current product epinephrine inhalation aerosol was reformulated with (b) (4) (HFA 134a) to replace the previously marketed products containing chlorofluorocarbons (CFC) as propellants. NDA 16126 (Wyeth) and ANDA 87907 (Armstrong) are withdrawn with the sunset of CFCs in inhalation products (See NDA 16126, DARRTS 12/11/2008 and ANDA 87907 DARRTS 8/29/14). Note that the current product is a suspension of epinephrine in HFA in a metal canister. The patient needs to rely on either the dose actuator indicator that is glued to the bottom of the canister and counts down from 160 in 20-spray increments, (b) (4) In contrast, the existing products were solutions of epinephrine in ethanol and CFC in a glass container with remaining medication visible to the patient. These product differences were discussed during the 2/25/14 Advisory Committee meeting during the first review cycle of NDA 205920.

Using the current suspension product, an HFA propelled inhalation aerosol, the patient needs to prime the inhaler (MDI) before inhaling the target dose of 125 mcg epinephrine per spray. Priming consists of shaking and spraying in the air before taking a dose (1-2 sprays). Because the suspension inherently settles upon standing, shaking and spraying before taking a dose is a critical instruction that the patient needs to understand and perform to receive a uniform dose. Initial priming and re-priming is indicated in similar prescription MDIs, but for prescription products, patients could receive counseling to understand and execute instructions for the patient (IFU). Clogging the mouthpiece orifice with residual product during use is typical for HFA MDIs and cleaning instructions are provided in the IFU. The drug product reviewer Dr. Ramaswamy analyzed the applicant's dose content uniformity studies in support of priming, re-priming and cleaning instructions. In addition, Dr. Ramaswamy compared this epinephrine MDI to approved prescription MDIs (label and IFU) and concluded that the current epinephrine MDI performs similarly to FDA approved prescription products. **See drug product review, pages 11-12**. Epinephrine inhalation aerosol was compared to seven approved products that are propelled with HFA and contain albuterol, fluticasone, ciclesonide or other drug combinations. The approved products are either rescue or maintenance medication and with the exception of ciclesonide solution all are suspensions. The epinephrine product is instructed for 4 initial primes, one reprime before each use and daily cleaning of the mouthpiece (if inhaler is used). These are conservative instructions as compared to the prescription products. The approved products are generally instructed for 3-4 initial primes, 1-4 reprimes of weekly-4weeks frequency and cleaning once a week. All suspension products require shaking before priming and dosing.

With respect to initial priming and effect on the dose **see drug product review p. 9-10.** Dr. Ramaswamy evaluated results presented by the applicant in reports QARD-009-16-00-FR and QARD- 009-16-02-FR, effect of initial priming on dose content uniformity through canister life and at beginning life stage. Failure to complete the initial priming sequence, shake and spray 4 times, may result in dispensing a non-uniform dose. If the 4 prime sequence is performed incorrectly with only initial shaking, and extended time to execute the 4 sprays, this may result in a hyper-potent dose of (b) (4)% label claim (LC) which is outside the acceptance criteria of dose content uniformity (DCU) (b) (4)% LC. Optimal priming occurs within (b) (4)sec and results in acceptable DCU. DCU remains within acceptance criteria through canister life even if time of initial timing sequence is varied **see drug product review p. 10.**

With respect to repriming (shake and spray in the air) before each use, this is a unique and conservative instruction for epinephrine. The canister has a capacity of 164 sprays and after the initial 4 primes, 160 sprays remain. The number of doses will be reduced with the proposed reprimes before every use and the lifetime of the product would be limited to <10 days if used at the rate of 8 puffs per day. This outcome was discussed with the clinical team during this review cycle and limiting the number of doses in the inhaler was considered appropriate.

With respect to cleaning the mouthpiece to prevent clogging **see drug product review p. 5-9.** Dr. Ramaswamy evaluated results presented by the applicant in cleaning procedure reports QARD-018-14-00-FR, QARD-018-14-01-FR and QARD-018-14-02-FR. DCU data indicated that use of the inhaler beyond 2 days (8 puffs/day

for 2 days) results in inconsistent dosing because of clogging. If the actuator is not washed, dosing becomes more variable though the mean delivery (DCU) remains close to target. The applicant varied cleaning of the mouthpiece to wash in up and down directions, with water, soapy water, wash time up to 30 sec, temperature 10-50ºC, air dry, dry with paper towel, lint free cloth, wet unit/reprime. For every condition, effectivenes of cleaning was assessed by testing n=10 inhalers for DCU after single prime and 2 days of simulated use (24 doses dispensed). DCU remained acceptable after a minimum of 2 sec rinse and was not impacted by water temperature or drying time. The instruction for cleaning is currently to "run water through (b) (4) the mouthpiece for 30 secs (b) (4) air dry overnight". This is a conservative instruction and sufficient to prevent clogging.

With respect to robustness of the dose (actuator) indicator (DI) **see drug product review p. 3-5 and p. 12-13**. Dr. Ramaswamy evaluated the applicant's response to establish acceptance criteria for count accuracy for the (b) (4) top mounted actuator indicator and reviewed the supporting DMF (b) (4) (see review in DARRTS 11/15/16). Dose accuracy is a critical attribute because the dose indicator counts down from (b) (4) to zero. When the dose indicator reaches 20-0 a red band appears to prompt the patient that the medication is depleted. The applicant proposed an accuracy quality limit (AQL) of (b) (4) which allows zero defects and to reject the lot if one unit is found defective. (A sample of 50 units is tested from a (b) (4) unit lot). Interpretation of the dose indicator reading, reliance on the indicator if dropped, and proper actuation (placement of the finger on the dose indicator during each actuation) are label comprehension deficiencies raised in the CR letter of 5/22/14 during first review cycle. The applicant performed additional drug product characterization to simulate product performance if patients deviate from labeling instructions. The reliability of the dose indicator was presented in study QARD-013-11-00FR in the original submission for n=90 inhalers dropped from 1m height on a concrete floor, DI facing up or down. The resubmission included data from 600 units assembled with or without the actuator dropped from 5ft with the DI facing up, down or horizontal, study QAPO-007-14-00-FR dated 11/26/14. The purpose was to simulate conditions of actual use, drop during disassembling, re-assembling, cleaning. The units were visually examined for damage and tested for count accuracy, valve and DI force characterization tests and shot weight accuracy. Units dropped assembled were not damaged and units dropped without the mouthpiece passed 98.2%. Accuracy count of the damaged units showed over counting by 1-3 counts but no undercounting. Shot weight analysis results were within the acceptable range of (b) (4) mg after one spray. (b) (4) Force tests were within corresponding specification and no overlap was observed between force to actuate (FTA) the indicator and MDI valve and force to fire (FTF). Overlap would imply undercount. The current labeling instruction (b) (4) Dr. Ramaswamy pointed out that the prescription products Alvesco (ciclesonide) and Bevespi Aerosphere (glycopyrrolate and formoterol fumarate) use similar dose indicators (**see drug product review and**

figure p. 12-13) and emphasize actuation by keeping the finger on the center to avoid off-center actuation.
The conclusion of the drug product review is that the product performs as expected of HFA MDIs and that the labeling instructions for use are supported by sufficient CMC characterization data. The ability of the patients to comprehend and execute these instructions in the OTC setting without counseling and physician supervision is critical to achieve the expected product performance. The suitability of this product for OTC use is deferred to the clinical team's evaluation and the assessment of the human factors studies and label comprehension studies.

With respect to cGMP compliance of manufacturing facilities **see facilities review**. The facilities reviewer Mr. Carl Lee discussed inspection results for the drug substance manufacturer (b) (4) to address GMP deficiencies cited in the CR letter. Armstrong Pharmaceuticals, Inc. (FEI: 3007009553), the drug product manufacturer was inspected during first cycle and is acceptable by profile. The CDRH-OC inspectional memorandum (see DARRTS 12/1/2016) for compliance of the device with device regulations determined that no pre-approval inspection was required as the recent Drug GMP inspection of the firm covered elements that demonstrated compliance of the facility and the device.
With regards to the documentation submitted for review, some documentation deficiencies were identified to applicable 21 CFR part 820 regulations for this combination product. Those deficiencies were noted in the review memo for documentation and incorporation into a post-approval inspection assignment.

C. Special Product Quality Labeling Recommendations (NDA only)

1. During labeling discussions, the drug product reviewer pointed out that (b) (4) . The DNDP labeling team proposed "spray indicator" because the indicator will count down reprimes and doses (sprays). CMC is in agreement with "spray indicator" for this OTC product because of the labeling instruction unique to this product and patient understanding.
2. (b) (4) to be removed from the established name line.

D. **Final Risk Assessment:** See discussion of residual risk in executive summary above.

Danae D. Christodoulou -S

Digitally signed by Danae D. Christodoulou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -S
Date: 2016.12.02 16:20:18 -05'00'

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

NDA 205-920

Trade Name (Epinephrine) Inhalation Aerosol

Armstrong Pharmaceuticals, Inc.

Sheldon Markofsky, Ph.D.
Muthukumar Ramaswamy, Ph.D.

Office of New Drug Quality Assessment

Chemistry Review for Division of Non-Clinical Prescription and Evaluation

Table of Contents

Chemistry Assessment Section

Chemistry Review Data Sheet

1. NDA 205920

2. REVIEW #: 1

3. REVIEW DATE: 4-24-14

4. REVIEWER: Sheldon Markofsky, Ph.D.: Muthukumar Ramaswamy, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 074286	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	07/22/13
CMC Information Amendment	2/07/14 2/24/14; 3/18/14; 3/26/14; 4/14/14

7. NAME & ADDRESS OF APPLICANT:

Name:	Armstrong Pharmaceuticals, Inc.
Address:	25 John Road, Canton, MA 02021
Representative:	Stephen Campbell, Amphastar Pharmaceuticals, Inc., 1170 6th Street, Rancho Cucamonga, CA
Telephone:	909-980-6422

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: [redacted] (b) (4) (**proposed but not finalized**)
b) Non-Proprietary Name (USAN): Epinephrine Inhalation Aerosol
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of Asthma

11. DOSAGE FORM: Aerosol

12. STRENGTH/POTENCY: 125mcg/spray

13. ROUTE OF ADMINISTRATION: Inhalation

14. Rx/OTC DISPENSED: ___Rx __X_OTC

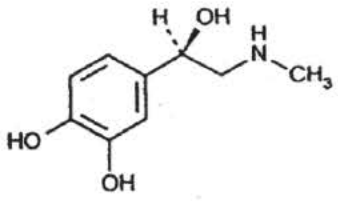
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

___SPOTS product – Form Completed

_X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name/Structure: (R)-(2) (-)-3,4-Dihydroxy- α -[(methylamino)methyl]benzyl alcohol.



Molecular formula: $C_9H_{13}NO_3$; Molecular Weight: 183.2

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	NA	Letter dated Feb

(b) (4)		(b) (4)				
						23, 2009.; Recent review in DARRTS 7/15/13
	IV		3	Adequate	NA	Letter dated May 18, 2010; Last review in DARRTS 2/15/12
	III		4	Adequate	NA	July 28, 2009
	III		4	Adequate	NA	Letter dated 3/4/09 10/03/12
	III		1,4	Adequate	NA	Letter dated 3/04/13
	III		3,4	Adequate	NA	Letter dated 3/04/13
	III		3, 4	Adequate	NA	Letter dated 10/03/12
	III		4	Adequate	NA	02/22/12, 1/26/11
	III		4	Adequate	NA	08/11/11
	V		3	Adequate	NA	LOA date: 03/08/13 Dr. Harrouk Filing review dated 9/19/13

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	074286	Epinephrine Inhalation aerosol
NDA	016126	Primatene Mist (Inactive)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable		
EES	Pending	04/15/14	
Pharm/Tox. (Extractables0	Review pending	4/18/14	Wafa Harrouk
Biopharm	NA		
LNC	Acceptable	4/24/14	M. Ramaswamy; Established name: Epinephrine inhalation aerosol
Methods Validation	Not needed		
OPDRA	Not Applicable		
EA	Acceptable	NA	M. Ramaswamy (See EA section within this NDA review)
Microbiology	Acceptable	7-25-13	Dr. Bryan Riley

Chemistry Assessment Section

The Chemistry Review for NDA 205920

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From chemistry perspective, the CMC review team recommends the approval of Trade Name (epinephrine) inhalation aerosol This CMC recommendation does not incorporate any potential facility inspection issues. As of 4/20/14, an overall acceptable recommendation for facilities associated with the NDA from the Office of Compliance is pending. The drug substance manufacturer, (b) (4) was issued a Warning Letter in (b) (4), was re-inspected during (b) (4) and was given "Withold" recommendation on (b) (4)

A shelf-life of 24 months is granted for epinephrine HFA inhalation aerosol (125mcg per actuation/NLT 160 sprays)) filled in 14mL (b) (4) aluminum canister crimped with 50 µl (b) (4) metering valve (b) (4) and dispensed with (b) (4) actuator (b) (4) . Recommended storage condition is (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Epinephrine inhalation aerosol is proposed for OTC use for the treatment of mild symptoms of intermittent asthma. The drug Substance, epinephrine is a white or off-white (b) (4) substance. The substance is sensitive to light and oxygen. It is sparingly soluble in water, very slightly soluble in alcohol. It contains one chiral center, which is in R configuration. The (b) (4) drug substance (D_{99} < (b) (4) is white to almost powder, hygroscopic. *It is oxygen sensitive and susceptible to degradation.* Epinephrine has USP monograph

The proposed product, is an aerosol suspension of (b) (4) epinephrine filled in 14mL aluminum canister fitted with 50µl (b) (4) metering valve (b) (4) actuator/mouthpiece. The aerosol suspension contains (b) (4) epinephrine (b) (4)%), polysorbate 80 (b) (4)%), ethanol (1%), thymol (b) (4)%), and HFA134 propellant (b) (4)%, a non-CFC propellant).

When used with a (b) (4) actuator (b) (4) the metered dose inhaler (MDI) unit is capable of delivering NLT 160 actuations, with each actuation consisting of 125 mcg of epinephrine emitted from the mouthpiece (label claim). The MDI assembly also contains a dose counter from (b) (4) to indicate the number of doses remaining in the canister. The purpose of the dose counter is to warn the consumer to buy a new unit, when the unit is near exhaustion.

Drug Substance:

Epinephrine is a white to off-white substance, (b) (4) darkens on exposure to light and air. The drug substance contains (b) (4)

[redacted] Epinephrine is very slightly soluble in water and in alcohol; with acids, it forms salts that are readily soluble in water.

[redacted] epinephrine is manufactured by [redacted], and Armstrong Pharmaceuticals references [redacted]s DMF [redacted] for the CMC information related to the epinephrine drug substance. Based on the latest up-dates and chemistry reviews of this DMF, the [redacted] drug substance is adequate to support this NDA (205920).

[redacted] epinephrine is manufactured by Armstrong Pharmaceuticals, Inc. in Canton, Massachusetts for use in the manufacture of the drug product. The drug substance [redacted] the drug substance will be tested for identity, assay, impurities and particle size distribution per approved epinephrine specification. The [redacted] drug substance will be stored [redacted] The Applicant has validated the API [redacted] and included validation information for the process validation lots, which is acceptable.

The manufacturer's [redacted] retest date, based on data in DMF [redacted] is [redacted] from the manufacturing date; and [redacted] is considered the expiration period for epinephrine USP [redacted] Armstrong will retest the drug substance [redacted] not to exceed the expiration date or manufacturer's [redacted] retest date of the [redacted] epinephrine.

Drug Product: The NDA provides adequate description and composition of the proposed drug product. It contains information on the excipients and container closure system components used for manufacturing the product. The excipients used in the manufacture the drug product are compendial and the proposed levels of inactive ingredients are within the levels present in approved products. The excipients used in the epinephrine inhalation aerosol are known to be used in products administered by inhalation route [redacted]

The Applicant has identified the source for each excipient. With the exception of HFA 134a, all excipients used in manufacturing are tested for conformance to approved specification. HFA 134a is tested for identity and verified for conformance to proposed specification based on supplier Certificate of Analysis.

The NDA contains drawings and dimensional acceptance criteria for the packaging components and provides adequate reference DMFs for [redacted] valve [redacted] actuator (DMF [redacted] aluminum canisters (DMF [redacted]) and dose counter (DMF [redacted]). The NDA contains supplier qualification documentation to support the use of these components in manufacturing operation.

The choice and strength of the proposed formulation are based on an initial evaluation of four different strength epinephrine inhalation products (90, 125, 180, 250µg/actuation) in the IND phase. The 125mcg dose was used in Phase 3 development program and is proposed for the to-be-marketed product. The NDA contains data from product characterization studies to support the proposed label claim (125 mcg/inhalation), storage conditions (store [redacted]°C), the performance characteristics of the product and the labeling statements.

The NDA contains adequate description of the name and address of the manufacturing facility, and the equipment to be used for the manufacture of the drug product, copies of the executed batch production

records (stability batches), specifications and certificates of analysis for the components and excipients used for the manufacture of the stability batches.

The manufacturing process for epinephrine inhalation aerosol consists of (b) (4) The Applicant's proposed commercial manufacturing process (commercial scale: (b) (4) kg) is based on the process used for manufacturing pilot and clinical batches ((b) (4) kg). The proposed commercial scale process is validated using three consecutive validation batches and the validation strategy evaluated the process controls associated with each of the unit operation.

The Applicant has proposed adequate manufacturing and in-process control information to support the proposed NDA. The proposed in-process controls includ (b) (4)

The Applicant's proposed drug product specification includes the following attributes: (a) identity; (b) assay, (c) impurities, (d) shot weight (valve delivery), (e) dose content per actuation (delivered dose uniformity and delivered dose uniformity through life; also referred as dose content uniformity and dose content through container life within this document), (f) number of actuations per container, (g) aerodynamic particle size distribution (particle size grouping for coarse particle mass (CPM), fine particle mass (FPM), extra fine particle mass (EPM), and impactor sized mass (ISM), % respirable fraction (%RF), respirable dose (RD), mass balance, mass median aerodynamic diameter (MMAD) , and geometric standard deviation (GSD)), (h) pressure of the individual dose unit, (i) leak rate, (j) moisture content, (k) microbial load, (l) foreign particulate matter, and (m) spray pattern. The NDA contains adequate description of the test methods and method validation information for the tests used during release and stability. The proposed specification for the epinephrine inhalation aerosol is based on Applicant's *manufacturing experience and available stability data, which is acceptable.*

Per FDA recommendation, the Applicant revised the acceptance criteria for dose content uniformity (DCU) (b) (4) Applicant's revised specification (b) (4) Applicant also agreed to monitor the levels of all potential leachables present in the drug product during post-approval stability. One lot per year will be tested on post-approval stability.

The NDA contains adequate stability data from 3 commercial scale batches and 3 registration stability batches to support the requested 24 months shelf-life for the proposed product. Based on available stability data from 6 months of accelerated (40°±5°C/75%±5%RH) and 24 months of long-term storage at 25°±2°C/ 60%±5%RH for three batches of product filled in commercial packaging configuration, a 24 months of shelf-life is granted.

B. Description of How the Drug Product is Intended to be Used

The drug product is proposed for the treatment of mild symptoms of intermittent asthma and can be used day or night. (1) The epinephrine HFA inhaler must be shaken before use to achieve the correct dosing.

Priming: For first use, prime the container 4 times before use. (b) (4)

Dose inhalation: Place mouthpiece in mouth with lips closed around and inhale deeply, (b) (4)

Instructions for inhalation, cleaning, and dose unit assembly are reproduced in in Section IIA, Labeling for reference (NDA information amendment dated 4/18/14.)

Note that:

i. *Data from characterization studies supported the definite need to shake the suspension before use (i.e., shake the MDI unit for* (b) (4) *Failure to follow the instruction may result in the dispensing of low* (b) (4) *mcg) to very high dose* (b) (4) *mcg) of drug from a single actuation.*
ii. *Daily cleaning of the actuator mouthpiece is required to avoid clogging. Data from simulated use study results (effect of not cleaning the unit daily) indicated that continued use of inhaler without cleaning would result in inconsistent dose.*
iii. *NDA contains data to support the priming instructions: (1) acceptability of the dose dispensed after initial priming (fire 4 spray to waste), (2) prime once after a resting time of 48 hours (to avoid loss of prime), and (3) prime once if the mouthpiece is wet, or if the unit is dropped.*
iv. *The dose counter performance data provided in the characterization studies section (transportation studies and drop test) generally support the reliability of the dose counter under conditions examined in the study. The drop test results showed that the units will overcount (i.e.,* (b) (4) *. Therefore, the labelling statement,* (b) (4) *should be included as proposed.*

C. Basis for Approvability or Not-Approval Recommendation

From CMC perspective, the Application is recommended for approval pending overall cGMP recommendation by OC.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name:	Sheldon Markofsky, Ph.D. Muthukumar Ramaswamy, Ph.D.
Secondary Reviewers:	Craig Bertha, Ph.D.
Chemistry Team Leader:	Danae Christodoulou, Ph.D.

C. CC Block

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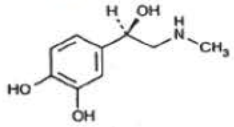
(b) (4)

Item	Information provided in NDA	Reviewer comment
Proprietary name and established name	(b) (4) (epinephrine)	Proposed label appears to be consistent with the labeling information (drug facts information) as required for OTC Bronchodilator Drug Products Subject to the 2011 Bronchodilator Final Rule –Reproduced
Dosage form and route of administration	Aerosol Inhalation	
Active moiety expression of strength with equivalence statement for salt (if applicable)	Epinephrine (125µg) Salt form not applicable	
Inactive ingredient information (quantitative, if injectables	Polysorbate 80 NF, Dehydrated alcohol USP	

21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Thymol NF HFA 134a	from Guidance for Industry: Labeling for Bronchodilators: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (Small Entity Compliance Guide) CDER, Nov. 2012.
Statement of being sterile (if applicable)	Not applicable	
Pharmacological/ therapeutic class	Bronchodilator	
Chemical name Structural formula Molecular Formula/Weight	Epinephrine  $C_9H_{13}NO_3$/ 183.2	
If radioactive, statement of important nuclear characteristics.	Not applicable	
Other important chemical or physical properties (such as pKa, solubility, or pH)	White or off-white (b) (4) substance, darkening on exposure to light and air. Very slightly soluble in water and in alcohol. Epinephrine is base. Slats are freely soluble in water. Pka is 8.59 at 25°C.	

Comments:

a) *Include instruction to shake the MDI unit* (b) (4)

b) Revise your storage instruction (b) (4) C.

(b) (4)

(b) (4)

[redacted]

B. Environmental Assessment (EA) Or Claim Of Categorical Exclusion: Adequate

"21 CFR §25.31 (a) states that exempted from EA can be granted if an Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety.

Armstrong Pharmaceuticals has requested categorical exemption from environmental impact analysis assessment on the following grounds:
Per Applicant, drug product, Epinephrine HFA MDI, does not contain ozone-depleting CFC propellants and has the same indications, lower level of dosage (125 mcg /inh. Used for E004 formulation vs. 225 mcg/inh. used for Primatene Mist formulation) (b) (4) [redacted] *to the applicant's knowledge, the data available do not establish that, at the expected level of exposure, the substance may be toxic to organisms in the environment.*

In addition, the Applicant's manufacturing facility located at Canton, MA complies with all federal, state and local environmental protection requirements and that it has a certified waste disposal program, and provided a Statement of Environmental Compliance in the NDA

Categorical exemption from environmental assessment under 21 CFR §25.31 (a) is acceptable.

III. List Of Deficiencies: None

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/s/

MUTHUKUMAR RAMASWAMY
04/24/2014

SHELDON B MARKOFSKY
04/24/2014

CRAIG M BERTHA
04/25/2014

DANAE D CHRISTODOULOU
04/25/2014
I concur with the reviewer's conclusions and recommendations

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 24 July 2013

TO: NDA 205920

FROM: Bryan S. Riley, Ph.D.
Team Leader (Acting)
OPS/New Drug Microbiology Staff

THROUGH: Stephen E. Langille, Ph.D.
Senior Review Microbiologist
OPS/New Drug Microbiology Staff

cc: Daniel Reed, MPH
Regulatory Project Manager
OND/DNCE

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for (b) (4) (Epinephrine Inhalation Aerosol) [Submission Date: 22 July 2013]

The Microbial Limits specification for (b) (4) is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

Primatene® HFA is a Metered Dose Inhaler for oral administration.

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

M E M O R A N D U M

Table 1 – Microbial Limits Specification

Test	Acceptance Criteria	Method
Total Aerobic Count	NMT (b) (4) CFU/mL	USP <61>
Total Yeast and Mold Count	NMT (b) (4) CFU/mL	USP <61>
S. aureus	Absent	USP <62>
Cl. Sporogenes	Absent	USP <62>
E. coli	Absent	USP <62>
P. aeruginosa	Absent	USP <62>
C. albicans	Absent	USP <62>
Salmonella species	Absent	USP <62>
Bile Tolerant Gram (-) bacteria	Absent	USP <62>

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The drug product will also be tested for Microbial Limits as part of the post-approval stability protocol.

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable testing protocol. The non-aqueous nature of the formulation also obviates the need for anti-microbial effectiveness testing.

END

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/s/

BRYAN S RILEY
07/24/2013

STEPHEN E LANGILLE
07/25/2013