CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205920Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	205920
Supporting document/s:	73
Applicant's letter date:	4 May 2018
CDER stamp date:	7 May 2018
Product:	Epinephrine inhalation aerosol (HFA MDI, 125 µg per inhalation)
Indication:	Temporary relief of mild symptoms of intermittent asthma
Applicant:	Armstrong Pharmaceuticals, Inc., a subsidiary of Amphastar Pharmaceuticals 25 John Road Canton, MA 02021
Review Division:	Nonprescription Drug Products
Reviewer:	D. Charles Thompson, RPh, PhD, DABT
Team Leader:	Jane J. Sohn, PhD
Division Director:	Theresa Michele, MD
Project Manager:	Helen Lee, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205920 are owned by Armstrong Pharmaceuticals, a subsidiary of Amphastar, Inc., for which the above-mentioned sponsor has obtained a written right of reference. Any information or data necessary for approval of NDA 205920 that the sponsor does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are included for descriptive purposes only and are not relied upon for approval of NDA 205920.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

NDA 205920 seeks approval of an epinephrine HFA MDI for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older in the OTC setting. The proposed HFA MDI drug product is the result of reformulation of an earlier marketed product with a CFC propellant.

1.2 Brief Discussion of Nonclinical Findings

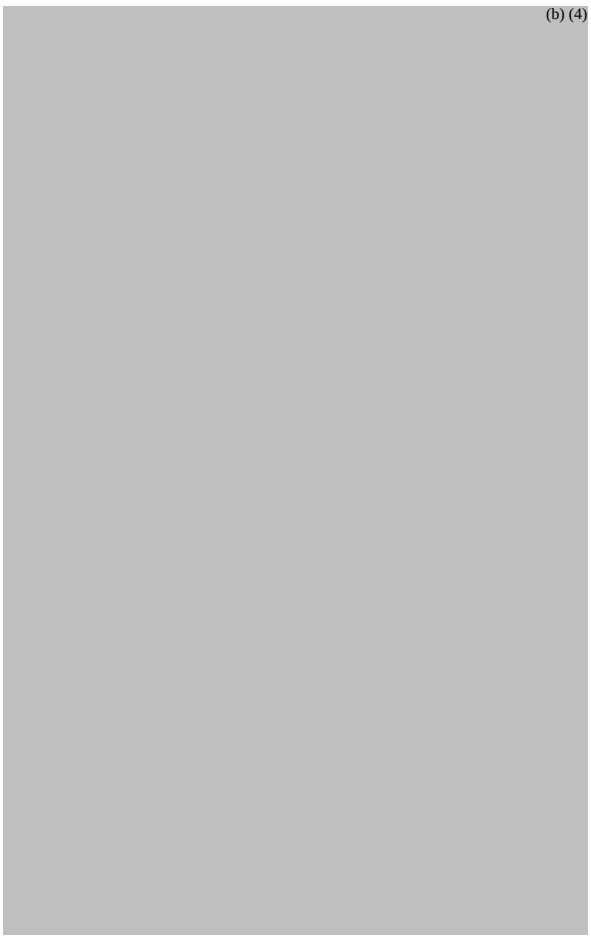
No nonclinical data were included in the submission and none were required.

1.3 Recommendations

1.3.1 Approvability: Approvable

1.3.2 Additional Nonclinical Recommendations: None

1.3.3 Labeling: None; the proposed labeling (see Sponsor's draft container label below) is considered adequate from a nonclinical perspective.



2 Drug Information

2.1 Drug

CAS Registry Number: 51-43-4

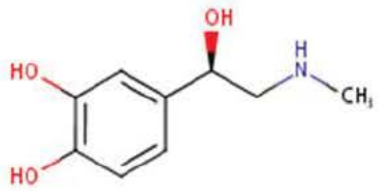
Generic Name: Epinephrine; adrenaline

Code Name: E400 (applicable to the Epinephrine HFA MDI)

Chemical Name: (-)-3,4-Dihydroxy-α-((methylamino)methyl)benzyl alcohol

Molecular Formula/Molecular Weight: $C_9H_{13}NO_3$/183.21

Structure:



Pharmacologic Class: alpha-/beta-adrenergic agonist; catecholamine

2.2 Relevant INDs, NDAs, BLAs and DMFs

The IND and MFs listed below are referenced by the Sponsor in the application; appropriate authorizations (LoAs) have been provided.

- IND 074286 for Epinephrine Inhalation Aerosol USP - Amphastar Pharmaceuticals, Inc.
- Type II DMF (b) (4)
- Type III DMF (b) (4)
- Type V (b) (4)
- Type III DMF (b) (4)
- Type IV DMF
- Type III DMF
- Type III DMF

- Type III DMF (b) (4)
- Type III DMF

2.3 Drug Formulation

The proposed drug product is an epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA) metered dose inhaler (MDI). The delivered dose is intended to be 125 µg/actuation of epinephrine. Drug product composition information remains unchanged from the previous review cycle; see previous review for additional details (D.C. Thompson, 16 November 2016).

2.4 Comments on Novel Excipients

No novel excipients are included in the drug product formulation. The safety of the thymol excipient for inhalation use has been adequately addressed (see previous review: D.C. Thompson, 16 November 2016).

2.5 Comments on Impurities/Degradants of Concern

None (see previous review: D.C. Thompson, 16 November 2016).

2.6 Proposed Clinical Population and Dosing Regimen

Epinephrine-HFA MDI is proposed for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. Recommended dosing is 1-2 inhalations as often as every 4 hours but not more than 8 inhalations in 24 hours.

2.7 Regulatory Background

Epinephrine has been marketed in the US for use in the treatment of asthma since the early 1900s. An oral MDI formulation utilizing a CFC propellant (Primatene® Mist) was approved for OTC use for the treatment of symptoms of asthma in 1967 under NDA 016126 (Wyeth), with subsequent approval of a generic version under ANDA 087997 (Armstrong) in 1984. Armstrong subsequently purchased the Primatene Mist trademark for their product and Wyeth discontinued their product.

MDIs using CFC propellants began to be phased out in 1996 to protect the environment under the Montreal Protocol on Substances that Deplete the Ozone Layer. A proposed rule for phase out of epinephrine CFC MDIs was published in 2007 and a Final Rule (2008) established 31 December 2011 as the end date for use of CFCs in epinephrine MDIs. Specifically, CFC-based Primatene® Mist was phased out of the US market in 2011.

IND 074286, providing for clinical development of a reformulated, non-CFC epinephrine MDI, was received on 26 October 2009 and allowed to proceed (Advice/Information Request letter, 23 December 2009). An initial NDA 205496 for Primatene® HFA (epinephrine inhalation aerosol USP, 125 µg/actuation) was received on 8 April 2013 and was not filed due to numerous deficiencies (Refusal to File letter, 7 June 2013). A

revised and new NDA 205920 was subsequently received on 22 July 2013. NDA 205920 was the subject of a Joint Meeting of the Nonprescription Drugs Advisory Committee (NDAC) and the Pulmonary-Allergy Drugs Advisory Committee (PADAC) on 25 February 2014.

An initial CR action was taken by DNDP in 2014 (Complete Response, 22 May 2014) for multiple deficiencies, including inadequate nonclinical safety support for use of thymol as an excipient in a chronically administered inhalation drug product. This nonclinical deficiency has now been adequately addressed by the Sponsor (see previous review: D.C. Thompson, 16 November 2016).

However, a second CR action was taken by DNDP for continuing clinical deficiencies relating to an inadequate human factors study and product labeling (Complete Response, 23 December 2016). The current submission constitutes the Sponsor's second Resubmission of NDA 205920 following Agency CR action.

3 Studies Submitted

No nonclinical data were included in the current resubmission and none were required.

3.1 Studies Reviewed

N/A

3.3 Previous Reviews Referenced

- NDA 205920: Pharmacology/Toxicology NDA Review and Evaluation, D.C. Thompson, RPh, PhD, DABT, 16 November 2016.

11 Integrated Summary and Safety Evaluation

NDA 205920 seeks approval of an epinephrine HFA MDI for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older in the OTC setting. The proposed HFA MDI drug product is the result of reformulation of an earlier marketed product with a CFC propellant.

NDA 205920 was originally received on 22 July 2013 and was the subject of a Joint Meeting of the Nonprescription Drugs Advisory Committee (NDAC) and the Pulmonary-Allergy Drugs Advisory Committee (PADAC) on 25 February 2014.

An initial CR action was taken by the Agency in May 2014, due to multiple deficiencies, among them inadequate nonclinical safety support for use of thymol as an excipient in a chronically administered inhalation drug product. This nonclinical deficiency has now been adequately addressed (see previous review: D.C. Thompson, 16 November 2016) and NDA 205920 is, thus, considered approvable from a nonclinical perspective.

There were, however, continuing clinical deficiencies with the initial resubmission relating to an inadequate human factors study and proposed drug product labeling (Complete Response, 23 December 2016). Please refer to reviews by the Clinical Review Team for assessments of the adequacy of the Sponsor's current resubmission to address these previously identified clinical deficiencies.

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/s/

DONALD C THOMPSON
07/10/2018

JANE J SOHN
07/10/2018
I concur.

AMENDED PHARMACOLOGIST REVIEW OF GLP EIR (CP 7348.808)

Firm Name: Amphastar Laboratories, Inc.
City, State: Chino, CA
EI Dates: October 17-21, 2016
FDA Participants: LCDR Marcus F. Yambot, Investigator, ORA/LOS-DO
Ke Zhang, PhD, CDER Pharmacologist
Zhou Chen, MD, PhD, CDER Pharmacologist

Inspection Summary

This was a FY2016 GLP directed inspection. At the close-out meeting on October 21, 2016 a 10-item Form FDA 483 was issued to the testing facility management. The OSIS review dated 11/25/2016 indicated that the firm's response to observations 5, 6c and 8 was inadequate and further corrective actions were required. The firm submitted an additional response on 12/12/2016. This reviewer considers the corrective actions in the firm's additional response to observations 5, 6c and 8 adequate. The final classification for this inspection is Voluntary Action Indicated (VAI). Based on the inspectional findings, this reviewer recommends that the three studies audited in the inspection be considered as non-GLP studies.

Study Audited during this Inspection

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

Background: Amphastar Laboratories, Inc. was founded in 2000 in Chino, CA and was then named the New Drug Research Center (NDRC). NDRC is a branch of Amphastar Pharmaceuticals, Inc. The major function of the NDRC facility is analytical testing for research chemistry, method development, formulation studies, and in vivo and in vitro early development pharmacological studies. Most studies conducted (more than 90%) are non-GLP studies. The species used in animal studies include rats, mice, rabbits, and dogs. Since 2005, the firm performed eight GLP studies and all those studies are related to human drugs.

The firm responded to the Form FDA 483 observations on November 9, 2016. Their response and proposed corrective actions to observations 5, 6c, and 8 were determined to be inadequate in the OSIS review dated 11/25/2016. This amendment provides an evaluation of the firm's additional written response to Form FDA 483 observations 5, 6c and 8 dated December 12, 2016.

OBSERVATION 5

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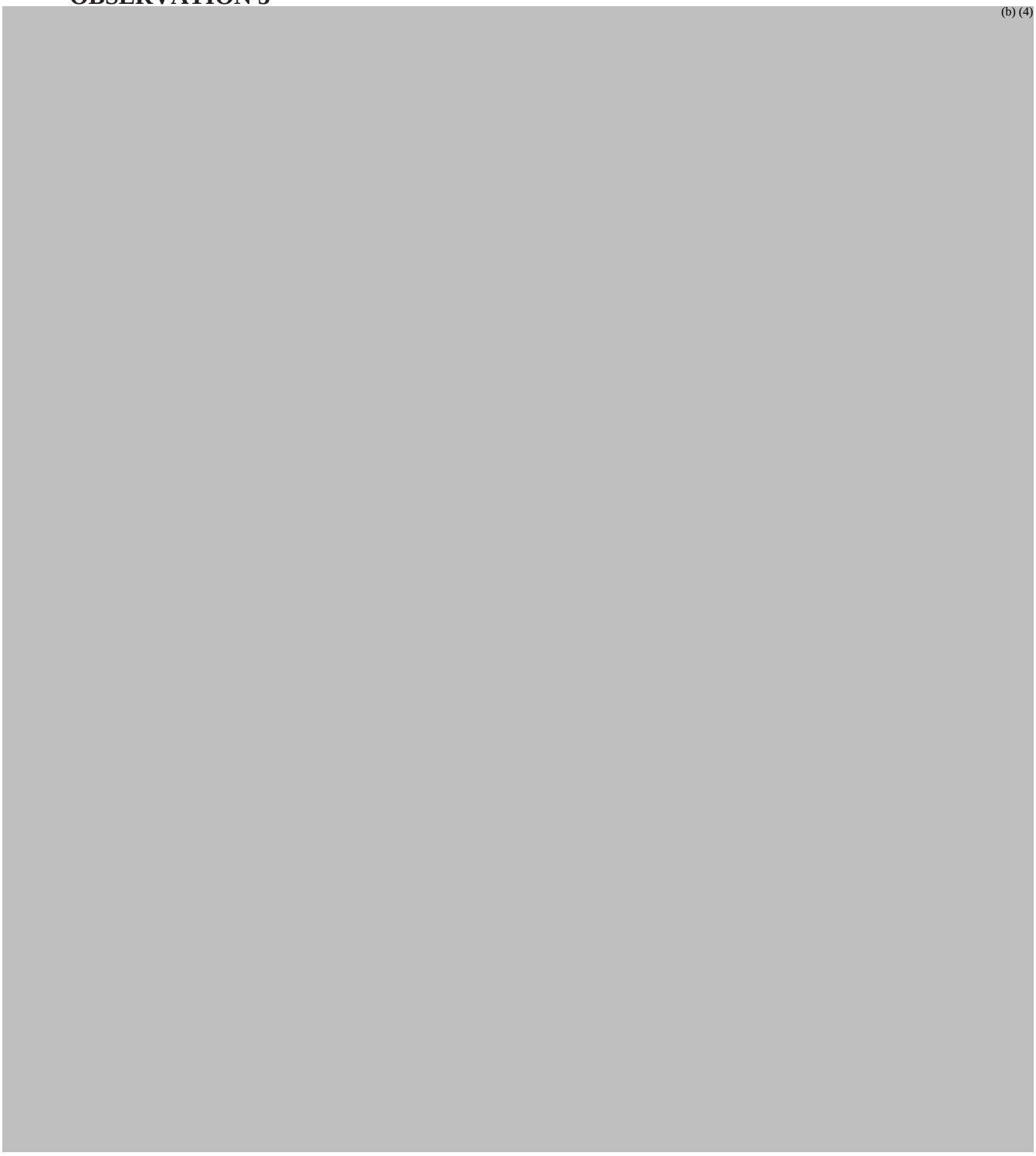

OBSERVATION 6

(b) (4)

OBSERVATION 8

(b) (4)

Zhou Chen, MD, PhD
Lead Pharmacologist

Date Assigned: 07/15/2016
EI Dates: 10/17-21/2016
District Office: LOS-DO
FDA Investigators: LCDR Marcus F. Yambot, LOS-DO
Ke Zhang, CDER Pharmacologist
Zhou Chen, CDER Pharmacologist

Inspection Type: _____Routine Surveillance __X__Directed
FDA-483 Issued: _____ No __X__Yes
Letter Issued: _____None __X__Inspection Response Request Letter

Date EIR Received by OSIS: 12/07/2016
Date EIR Received by Reviewer: 12/21/2016
1st Draft Review Completed: 12/29/2016

Inspection Conclusion: VAI
District Decision: VAI
Final HQ Classification: VAI

cc: via DARRTS

OSIS/Kassim/Nkah/Fenty-Stewart/Miller/Johnson
OSIS/DNDBE/Bonapace/ChenZ/ZhangK/Raha
DNDP/D. Charles Thompson/Pharmacologist (NDA 205920, IND 074286)
DNDP/Tinya J. Sensie/Regulatory Project Manager (NDA 205920)
DNDP/Daniel H. Reed/Regulatory Project Manager (IND 074286)
HFR-PA250/LCDR Marcus F. Yambot (ORA Investigator)
HFR-PA2535/Cynthia Myers (BIMO)
HFR-PA250/Monica Maxwell (DIB)
HFR-PA240/Kelly Sheppard (DCB)
Draft: ZC 12/29/2016
Edits: CB 1/3/2017
OSIS File: GLP0942
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/GLP Program/Amphastar Laboratories, Chino, CA/FY2016/ REVIEW (EIR COVER)

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/s/

ZHOU CHEN
01/05/2017

CHARLES R BONAPACE
01/05/2017

Secondary Pharmacology and Toxicology Review

NDA: 205920
CDER stamp date: June 28, 2016
Product: Epinephrine inhaled aerosol hydrofluoroalkane
Indication: Temporary relief of mild symptoms of intermittent asthma
Applicant: Armstrong Pharmaceuticals, Inc. (a subsidiary of Amphastar Laboratories, Inc.)
Author: Jane J. Sohn, Ph.D., Team Lead, Division of Nonprescription Drug Products

Introduction:
Epinephrine inhaled aerosol hydrofluoroalkane (HFA) is a fixed dose inhaler of epinephrine for the temporary relief of mild symptoms of intermittent asthma.

The applicant Armstrong Pharmaceuticals, Inc. (Armstrong) submitted data from studies in mice to qualify the excipient thymol. The Division of Nonprescription Drug Products (DNDP) requested a nonclinical site audit by the Office of Study Integrity and Surveillance (OSIS) to determine the reliability of the nonclinical data and confirm GLP-compliance.

Discussion:
DNDP reviewer Dr. D. Charles Thompson assessed the safety of thymol based on a summary report of 3 nonclinical studies (review dated November 16, 2016). He recommended that the proposed clinical use of thymol appears to be reasonably safe, considering the limited amount of thymol exposure expected, the previous human experience, and the absence of findings resulting from the chronic exposure of animals to high concentrations of thymol in excess of the proposed clinical exposure. This determination was pending the results of the nonclinical site audit.

Observations during the OSIS nonclinical site audit led to the following recommendations (review dated 11/25/16): "After evaluating the inspectional findings, the data from the three audited studies were found to be unreliable. Therefore, the three audited studies should not be considered GLP compliant studies and the data should be considered for reference purposes only." Further discussion with Dr. Zhou Chen of OSIS clarified that no fraudulent activities were found, although the clinical observations in the study were not reliable. Importantly, the tissue collection and histopathological samples were handled in a reliable manner. Dr. Chen did not recommend that the study be rejected, and supported using the nonclinical data in combination with clinical data for safety assessment. A Form FDA 483 was presented and discussed with the applicant, and the applicant's response to 3 observations was inadequate. The final classification of the inspection was Voluntary Action Indicated (VAI). Further corrective actions are required for the following issues (communication dated November 29, 2016):

The conclusions of the nonclinical site audit, and the analysis of the nonclinical study were discussed with the review team for this NDA on November 28, 2016. The clinical team determined that clinical

observations from a clinical study, which was reviewed in the first review cycle (review dated April 14, 2014), could be used to address the lack of clinical observations in the mouse study. Briefly, the applicant conducted a safety and efficacy study in which subjects received 4 doses daily of the proposed product for 12 weeks, followed by a 12 week safety follow up period.

Conclusion:
This NDA can be approved from the pharmacology/toxicology perspective and no additional nonclinical studies are needed. This decision relies upon the available nonclinical data, in combination with previous human experience reviewed by the clinical team.

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/s/

JANE J SOHN
11/30/2016

PHARMACOLOGIST REVIEW OF GLP EIR (CP 7348.808)

Firm Name: Amphastar Laboratories, Inc.
City, State: Chino, CA
EI Dates: October 17-21, 2016
FDA Participants: LCDR Marcus F. Yambot, Investigator, ORA/LOS-DO
Ke Zhang, PhD, CDER Pharmacologist
Zhou Chen, MD, PhD, CDER Pharmacologist

Inspection Summary

This was a FY2016 GLP directed inspection. At the close-out meeting on October 21, 2016 a 10-item Form FDA 483 was issued to the testing facility management. A summary of the observations includes the following:

(b) (4)

The final classification for this inspection is Voluntary Action Indicated (VAI). Based on the inspectional findings, this reviewer recommends that the three studies audited in the inspection be considered as non-GLP studies.

Study Audited during this Inspection

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

Background: Amphastar Laboratories, Inc. was founded in 2000 in Chino, CA and was then named the New Drug Research Center (NDRC). NDRC is a branch of Amphastar Pharmaceuticals, Inc. The major function of the NDRC facility is analytical testing for research

chemistry, method development, formulation studies, and in vivo and in vitro early development pharmacological studies. Most studies conducted (more than 90%) are non-GLP studies. The species used in animal studies included rats, mice, rabbits, and dogs. Since 2005, the firm performed eight GLP studies and all studies are related to human drugs.

Prior Inspection: This is the firm's first FDA GLP inspection.

The following concerns were received from the CDER Pharmacology/Toxicology reviewer to address during the inspection:

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[redacted]

Recommendations:

- After evaluating the inspectional findings, the data from the three audited studies were found to be unreliable. Therefore, the three audited studies should not be considered GLP-compliant studies and the data should be considered for reference purposes only.
- The next inspection should be scheduled based on the firm's GLP workload.
- Final classification: Voluntary Action Indicated (VAI).

Zhou Chen, MD, PhD
Lead Pharmacologist

Date Assigned: 07/15/2016
EI Dates: 10/17-21/2016
District Office: LOS-DO
FDA Investigators: LCDR Marcus F. Yambot, LOS-DO
Ke Zhang, CDER Pharmacologist
Zhou Chen, CDER Pharmacologist

Inspection Type: _____Routine Surveillance __X__Directed
FDA-483 Issued: _____ No __X__Yes
Letter Issued: _____None __X__Inspection Response Request Letter

Date EIR Received by OSIS: N/A
Date EIR Received by Reviewer: N/A
1st Draft Review Completed: 11/17/2016

Inspection Conclusion: VAI
District Decision: VAI
Final HQ Classification: VAI

cc: via DARRTS

OSIS/Kassim/Nkah/Fenty-Stewart/Miller/Johnson
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Draft: ZC 11/17/2016
Edits: CB 11/23/2016
OSIS File: GLP0942
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/GLP Program/Amphastar Laboratories, Chino, CA/FY2016/ REVIEW (EIR COVER)

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/s/

ZHOU CHEN
11/25/2016

CHARLES R BONAPACE
11/25/2016

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	205920
Supporting documents:	39, 48, and 59
Applicant's letter date:	28 June, 31 August, and 9 November 2016
CDER stamp date:	28 June, 31 August, and 9 November 2016
Product:	Epinephrine inhalation aerosol (HFA MDI, 125 µg per inhalation)
Indication:	Temporary relief of mild symptoms of intermittent asthma
Applicant:	Armstrong Pharmaceuticals, Inc., a subsidiary of Amphastar Pharmaceuticals 25 John Road Canton, MA 02021
Review Division:	Nonprescription Drug Products
Reviewer:	D. Charles Thompson, RPh, PhD, DABT
Team Leader:	Jane J. Sohn, PhD
Division Director:	Theresa Michele, MD
Project Manager:	Tinya Sensie, MHA

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1 Executive Summary

1.1 Introduction

NDA 205920 seeks approval of an epinephrine HFA MDI for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older in the OTC setting. The proposed HFA MDI drug product is the result of reformulation of an earlier marketed drug product with a CFC propellant.

The current submission constitutes the Sponsor's resubmission of the application following a CR action by the Division of Nonprescription Drug Products (DNDP) in which a primary deficiency identified was a lack of nonclinical safety support for the proposed formulation excipient, thymol, under chronic inhalation conditions of use. The CR letter stipulated that this deficiency be addressed by submission of a 6-month repeated dose inhalation toxicity study in an appropriate nonclinical species.

1.2 Brief Discussion of Nonclinical Findings

The submission is comprised of a single, summary report of two parallel, overlapping 6-month repeated dose inhalation toxicity studies in CD-1 mice, plus results of a separate toxicokinetic (TK) analysis in mice under comparable exposure conditions but conducted approximately 1.5 years after the chronic studies. On face, the study data provided suggest an absence of either local or systemic adverse effects in mice following repeated inhalation exposure for six months. However, the study design employed suffers from a number of deficiencies that are discussed in detail in this review. Additional deficiencies included lack of characterization of the nonclinical MDI test article. At FDA request, the Sponsor generated and submitted additional new data to address test article characterization. Based on these new test article characterization data, in conjunction with the levels of thymol detected in the animals in the ad hoc PK study, it is reasonable to conclude that the animals were exposed to thymol in a vapor phase at a concentration that was higher than the proposed clinical concentration.

1.3 Recommendations

1.3.1 Approvability: The chronic inhalation toxicity studies described by the Sponsor in the original NDA resubmission fail to meet generally accepted scientific and regulatory standards for study design and conduct. However, taking into consideration all original and subsequent information that the Sponsor has submitted, in conjunction with all other available safety information on thymol and the low clinical exposure levels anticipated, the proposed clinical use level of (b) (4) % thymol as an excipient appears to be reasonably safe from a nonclinical perspective. This decision is pending a final reporting from the OSIS GLP inspection of the nonclinical test facility.

1.3.2 Additional Non Clinical Recommendations: None

2 Drug Information

2.1 Drug

CAS Registry Number: 51-43-4

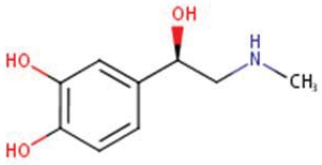
Generic Name: Epinephrine; adrenaline

Code Name: E400 (applicable to the Epinephrine HFA MDI)

Chemical Name: (-)-3,4-Dihydroxy-α-((methylamino)methyl)benzyl alcohol

Molecular Formula/Molecular Weight: $C_9H_{13}NO_3$/183.21

Structure:



Pharmacologic Class: alpha-/beta-adrenergic agonist; catecholamine

2.2 Relevant INDs, NDAs, BLAs and DMFs

The IND and MFs listed below are referenced by the Sponsor in the application; appropriate authorization (LoAs) are provided.

- IND 074286 for Epinephrine Inhalation Aerosol USP - Amphastar Pharmaceuticals, Inc.
- Type II DMF (b) (4)
- Type III DMF
- Type III DMF
- Type III DMF
- Type III DMF
- Type III DMF
- Type III DMF
- Type III DMF
- Type IV DMF
- Type V DMF

2.3 Drug Formulation

The proposed drug product is an epinephrine inhalation aerosol hydrofluoroalkane (epinephrine-HFA) metered dose inhaler (MDI). The unit dose composition of the product, which is (b) (4) suspension, is summarized in the Sponsor's Table 2.3.P-3 below. The delivered dose is intended to be 125 µg/actuation of epinephrine.

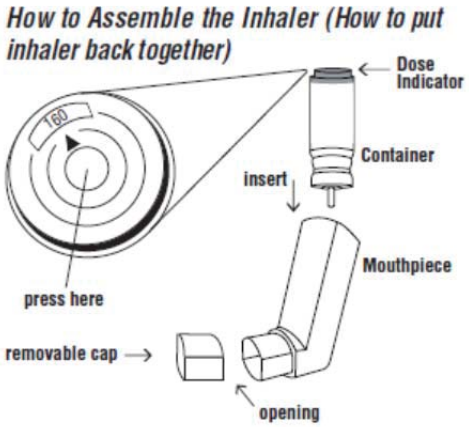
Table 2.3.P-3 Unit Dose Compositions of the proposed Product, Epinephrine HFA MDI

Strength		125 mcg/spray
Unit Composition (% w/w)		
API:		
Epinephrine USP, (b) (4) (free base)		(b) (4)
Inactive Ingredients:		
(b) (4)	Polysorbate 80, NF	
	Dehydrated alcohol USP	1.0000
	Thymol NF	(b) (4)
(Propellant)	HFA-134a	
Filling amount, g/unit		(b) (4) (target)
(b) (4)		

The proposed epinephrine HFA MDI includes a 14 mL anodized aluminum canister with metering valve (b) (4), a top mounted dose indicator (b) (4) and an orange L-shaped actuator (b) (4) with a red dust cap (see Sponsor's proposed labeling schematics below).

Figure 2 Proposed Product Package for E004

(b) (4)



ONDQA Chemistry review of the original application concluded overall that "...the Application is recommended for approval pending overall cGMP recommendation by OC (Markofsky and Ramaswamy, 25 April 2014; see Section 3.3 below). Of particular relevance, the review provided the following summary comments:

> "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) (b) (4) (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) at release and through container life; Applicant's revised specification included particle size grouping acceptance criteria for the average mass of drug substance collected on various stages of Andersen multistage cascade impactor. 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 Applicant's revised product specification is

acceptable and consistent with the principles outlined in draft MDI (1998) guidance, and Applicant's stability data."

	(b) (4)	Pressure	Assay	Particle Size Distribution					
				MMAD	sigma, GSD	RF%	RD, µg	Mass balance	Leak Rate, mg/year
Max.	(b) (4)								(b) (4)
Min.									
Mean	303.6	79.2	31.44	1.99	1.76	67	86	103	261
Std. dev.	88.9	1.7	0.4	0.07	0.05	2.3	4.6	4.7	
mean + 3 SD	**570.3**	**84.3**	**32.64**	**2.2**	**1.91**	**73.9**	**99.8**	**117.1**	
mean + 3 SD		**74.1**	**30.24**	**1.78**	**1.61**	**60.1**	**72.2**	**88.9**	

	Foreign particles			Spray Pattern (ovalality ratio)		major axis		
								Thymol %
Max.	(b) (4)							(b) (4)
Min.								
Mean	28.1	7.1	2.2	1.14	1.14	14.3	18.4	0.0091
Std. dev.	26.6	7.3	2.4	0.05	0.05	1	1.1	0.0004
mean + 3 SD	**107.9**	**29**	**9.4**	**1.29**	**1.29**	**17.3**	**21.7**	**0.0103**
mean + 3 SD	**-51.7**	**-14.8**	**-5**	**0.99**	**0.99**	**11.3**	**15.1**	**0.0079**

Applicant's revised drug product acceptance criteria for particle size cascade impaction is shown below.

	(b) (4)
Particle Size Cascade Impaction	

2.4 Comments on Novel Excipients

No novel excipients were identified in the proposed drug formulation. However, thymol has not previously been used in an inhalation drug product approved for a chronic indication (see previous review, Section 3.3 below: NDA 205920, W. Harrouk, PhD, 2 May 2014).

The Sponsor's submitted nonclinical summary report states on page 10 that "the delivered amount of thymol would be [redacted] mcg per single actuation." However, OPQ reviewers (Markofsky and Ramaswamy, 25 April 2014) concluded the amount of thymol delivered would be closer to [redacted] ug as summarized below.

> Evaluation: Adequate with comment. The composition of the E004 formulation per actuation is not disclosed in the NDA. Since a 50µL metering valve is used for delivering the E004 formulation, the amount of drug delivered per actuation will be [redacted] The CMC reviewer calculated the composition of the E004 formulation delivered per actuation (see table below):

Ingredient	% Composition	Approximate Amount present/actuation
Epinephrine	[redacted]	[redacted]
Polysorbate 80		
Dehydrated alcohol		
Thymol		
HFA-134a		

2.5 Comments on Impurities/Degradants of Concern

Refer to previous review as referenced in Section 3.3 below: NDA 205920, W. Harrouk, PhD, 2 May 2014.

2.6 Proposed Clinical Population and Dosing Regimen

Epinephrine-HFA MDI is proposed for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older. Recommended dosing is 1-2 inhalations as often as every 4 hours but not more than 8 inhalations in 24 hours. Patients are warned to consult a physician if they experience more than 2 asthma attacks in a week, which would equate practically with a maximum of 16 inhalations per week. Importantly, DNDP has determined that epinephrine HFA, while used intermittently, is considered to be for chronic use because consumers can use it repeatedly over a lifetime (T.M. Michele, 22 May 2014).

2.7 Regulatory Background

Epinephrine has been marketed in the US for use in the treatment of asthma since the early 1900s. An oral MDI formulation utilizing a CFC propellant (Primatene® Mist) was approved for OTC use for the treatment of symptoms of asthma in 1967 under NDA 016126 (Wyeth), with subsequent approval of a generic version under ANDA 087997 (Armstrong) in 1984. Armstrong subsequently purchased the Primatene Mist trademark for their product and Wyeth discontinued their product.

MDIs using CFC propellants began to be phased out in 1996 to protect the environment under the Montreal Protocol on Substances that Deplete the Ozone Layer. A proposed rule for phase out of epinephrine CFC MDIs was published in 2007 and a Final Rule

(2008) established 31 December 2011 as the end date for use of CFCs in epinephrine MDIs. Specifically, CFC-based Primatene® Mist was phased out of the US market in 2011.

IND 074286, providing for clinical development of a reformulated, non-CFC epinephrine MDI, was received on 26 October 2009 and allowed to proceed (Advice/Information Request letter, 23 December 2009). An initial NDA 205496 for Primatene® HFA (epinephrine inhalation aerosol USP, 125 µg/actuation) was received on 8 April 2013 and was not filed due to numerous deficiencies (Refusal to File letter, 7 June 2013). A revised and new NDA 205920 was subsequently received on 22 July 2013. NDA 205920 was the subject of a Joint Meeting of the Nonprescription Drugs Advisory Committee (NDAC) and the Pulmonary-Allergy Drugs Advisory Committee (PADAC) on 25 February 2014.

Following internal review, teleconference (Internal Meeting Minutes, 7 May 2014) and IR letter (Information Request, 9 May 2014) communications were issued to the Sponsor outlining a number of deficiencies with their application—including a lack of safety support for use of thymol as an excipient in a chronically administered inhalation drug product. Additional information was received from the Sponsor on 12 May 2014 (Response to Information Request, SDN-36). This information was determined to be inadequate (Nonclinical Primary Review, 20 May 2014).

For this and other product quality/clinical deficiencies, a Complete Response action was communicated to the Sponsor (Complete Response, 22 May 2014). In this and subsequent face-to-face communications (Meeting Minutes, 30 October 2014), the Sponsor was advised that a repeated dose inhalation toxicity study of 6 months duration in an appropriate species demonstrating no adverse findings is needed to support the use of thymol as an excipient in their HFA MDI product.

The Sponsor elected to initiate two separate 6-month inhalation toxicity studies in mice, the first (E004-VO-002) in September, 2014, and the second (E004-VO-003) in October, 2014. A protocol for the first study (E004-VO-002) was submitted to FDA for comment under IND 074286 after both studies had already begun (SDN-92, received 1 December 2014). Following internal review (NDA 205920, W. Harrouk, 7 April 2015), an advice letter with comments on the protocol was issued to the Sponsor (IND 074286, Advice Letter, 22 January 2016).

The Sponsor's Resubmission of NDA 205920 in response to the Agency's CR Action was received on 28 June 2016 (SDN-39); additional nonclinical information was received on 31 August 2016 (SDN-48) and on 9 November 2016 (SDN-59) in response to IRs. These data are reviewed below.

DNDP consulted the Office of Study Integrity and Surveillance (OSIS) to conduct a nonclinical inspection to confirm the GLP-compliance of pivotal nonclinical studies to support the safety of chronic inhalation use of thymol (study numbers E004-VO-002, E004-VO-003, and E004-VO-005). An inspection was performed the week of 17

October 2016. A final reporting of OSIS findings from the inspection is pending submission under this NDA.

3 Studies Submitted

3.1 Studies Reviewed

- Studies E004-VO-002, E004-VO-003, and E004-VO-005: Summary Report for Six-Month Chronic Toxicity Studies of Thymol by Inhalation—Chronic Toxicity Studies of Inhaled Thymol on the Lung and Respiratory Tract in the Mouse Model.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

- NDA 205920: Protocol No. E004-VO-002: Chronic Toxicity of Thymol on Lung and Respiratory Tract, Wafa Harrouk, 7 April 2015
- NDA 205920: Summary Review for Regulatory Action, Theresa M. Michele, MD, 22 May 2014.
- NDA 205920: Pharmacology/Toxicology NDA Review Addendum, Wafa Harrouk, PhD, 20 May 2014.
- NDA 205920: Pharmacology/Toxicology NDA Review and Evaluation, Wafa Harrouk, PhD, 2 May 2014.
- NDA 205920: Chemistry Review, Sheldon Markofsky, PhD, and Muthukumar Ramaswamy, PhD, 25 April 2014.
- NDA 205920: Pharmacology/Toxicology Filing Checklist for a New NDA, Wafa Harrouk, PhD, 19 September 2013.
- IND 074286: Pharmacology/Toxicology Safety Review, Xinguang (Cindy) Li, PhD, 25 November 2009.
- PIND 074286: Medical Officer Review, Theresa M. Michele, MD, 30 November 2008.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: Summary Report for Six-Month Chronic Toxicity Studies of Thymol by Inhalation: Chronic Toxicity Studies of Inhaled Thymol on the Lung and Respiratory Tract in the Mouse Model

Study no.:	E004-VO-002, E004-VO-003, and E004-VO-005
Study report location:	EDR
Conducting laboratory and location:	Amphastar Laboratories, New Drug Research Center, Chino, CA, USA
Date of study initiation:	September/October, 2014, for the two 6-month toxicity studies; May, 2016, for the PK study
GLP compliance:	TBD (pending findings from 17 October 2016 OSIS inspection)
QA statement:	Yes
Drug, lot #, and % purity:	E004 HFA MDI test products, formulated without epinephrine as summarized in the Sponsor's Table 3 below. Test article lot numbers were PL000114 (vehicle control), PL000314 (Article 1, (b) (4) % thymol), and PL00414 (Article 2, (b) (4) % thymol). The report states that "All three (3) test articles (Vehicle, Article-1, and Article-2) were prepared by Armstrong Pharmaceuticals, Inc., the manufacturer of E004 under GMP conditions. The amount of thymol in these articles was tested before their release by Armstrong. At the end of the 6-month studies, Armstrong retested these articles, and confirmed good stability of thymol with all specifications met [sic]." No CoA or assurance of quality was otherwise provided.

Table 3 Formulations of E004 and Study Articles

Items	E004 125mcg/spray	Study Materials		
		Vehicle Control	Article 1	Article 2
Product Description				
Description	Normal E004	Thymol-eliminated E004 Placebo	Thymol-Strengthened E004 Placebo	
Thymol Relative Amount*		(b) (4)		
Formulation, as w/w%				
Epinephrine				
Polysorbate 80				
Ethanol				
Thymol				
HFA-134a				
Thymol Delivered				
Thymol per spray**, mcg				
Thymol for 15 spray**, mcg				

* Relative to the amount of thymol delivered by E004 per spray
** The amount delivered out of actuator

Key Study Findings

- All animals survived to scheduled necropsy.
- No clinical observations were reported in any study animal.
- No effects of drug treatment on body weight, food consumption, or gross or microscopic findings in respiratory tissues were reported.
- The study is considered deficient for the following reasons:
  - Exposure chamber aerosols were not continuously generated throughout duration of animal exposures.
  - No concurrent and repeated assessment of exposure chamber concentrations.
  - No concurrent and repeated assessment of exposure aerosol APSD.
  - No continuous airflow through the exposure chambers; humidity and oxygen concentration were not monitored and reported.
  - Exposure duration of 10 minutes/day, 3 days/week is less than the maximum feasible duration and frequency of exposure.
  - Number of animals (8/sex/group) is not optimal.
- The ad hoc PK study confirmed systemic exposure of animals to thymol.
- Final determination as to the reliability of the study data for regulatory decision-making will be dependent upon findings from an unannounced OSIS GLP inspection of the test facility, conducted the week of 17 October 2016.

Methods

Doses:	0 (air), 0 (vehicle), (b) (4) % thymol in HFA MDI formulation (see Sponsor's Table 4 summary below)
Frequency of dosing:	3 exposure sessions per week for 26 weeks (78 total exposures) in each of two separate studies
Route of administration:	Nose-only inhalation via exposure chamber (see Sponsor's Figures 2 and 3 and related discussion of exposure assessment below)
Dosing Duration:	10 minutes per session
Formulation/Vehicle:	Polysorbate 80, ethanol, and HFA-134a propellant
Species/Strain:	Mouse/CD-1
Number/Sex/Group:	8/sex/group in each of two 6-month studies
Age:	5-8 weeks at dosing initiation
Weight:	28-36 g (M); 23-32 g (F)
Satellite groups:	8/sex/group for TK sampling
Unique study design:	Two separate, staggered and parallel 6-month studies were conducted: 'Set-1' initiated dosing on 22 Sept 2014 and ended dosing on 20 Mar 2015; 'Set-2' initiated dosing on 15 Oct 2014 and ended dosing on 13 April 2015. The data from the two studies were pooled for analysis and reporting (not described in protocol amendment). Plasma drug concentrations were not assessed in concurrent satellite TK animals; rather, a separate PK study was conducted in May, 2016.
Deviation from study protocol:	Not reported

Table 4 Treatment Groups and List of Animals

Study Sets	Set-1 Protocol: E004-VO-002				Set-2 Protocol: E004-VO-003			
Group No.	1	2	3	4	1	2	3	4
Article and Treatments								
Article Name	Air	Vehicle	(b) (4) Thymol	Thymol	Air	Vehicle	(b) (4) Thymol	Thymol
Article Lot No.	-	PL000114	PL000314	PL00414	-	PL000114	PL000314	PL00414
# of weeks for treatment	26	26	26	26	26	26	26	26
# of treatments per week	3	3	3	3	3	3	3	3
Total # of treatments	78	78	78	78	78	78	78	78
Mice information								
# of Male Mice	8	8	8	8	8	8	8	8
# of Female Mice	8	8	8	8	8	8	8	8
Subtotal # of Mice	16	16	16	16	16	16	16	16
Mice ID (Male)	174-11M1	174-13M1	174-15M1	174-17M1	176-11M1	176-13M1	176-15M1	176-17M1
	174-11M2	174-13M2	174-15M2	174-17M2	176-11M2	176-13M2	176-15M2	176-17M2
	174-11M3	174-13M3	174-15M3	174-17M3	176-11M3	176-13M3	176-15M3	176-17M3
	174-11M4	174-13M4	174-15M4	174-17M4	176-11M4	176-13M4	176-15M4	176-17M4
	174-12M1	174-14M1	174-16M1	174-18M1	176-12M1	176-14M1	176-16M1	176-18M1
	174-12M2	174-14M2	174-16M2	174-18M2	176-12M2	176-14M2	176-16M2	176-18M2
	174-12M3	174-14M3	174-16M3	174-18M3	176-12M3	176-14M3	176-16M3	176-18M3
	174-12M4	174-14M4	174-16M4	174-18M4	176-12M4	176-14M4	176-16M4	176-18M4
Mice ID (Female)	174-01F1	174-03F1	174-05F1	174-07F1	176-01F1	176-03F1	176-05F1	176-07F1
	174-01F2	174-03F2	174-05F2	174-07F2	176-01F2	176-03F2	176-05F2	176-07F2
	174-01F3	174-03F3	174-05F3	174-07F3	176-01F3	176-03F3	176-05F3	176-07F3
	174-01F4	174-03F4	174-05F4	174-07F4	176-01F4	176-03F4	176-05F4	176-07F4
	174-02F1	174-04F1	174-06F1	174-08F1	176-02F1	176-04F1	176-06F1	176-08F1
	174-02F2	174-04F2	174-06F2	174-08F2	176-02F2	176-04F2	176-06F2	176-08F2
	174-02F3	174-04F3	174-06F3	174-08F3	176-02F3	176-04F3	176-06F3	176-08F3
	174-02F4	174-04F4	174-06F4	174-08F4	176-02F4	176-04F4	176-06F4	176-08F4

Figure 2 Breathing Tank Used for Thymol Inhalation

(b) (4)

Figure 3 Pictorial Representation of Components on the Breathing Tank

Study Apparatus

The report states that the study employed two separate breathing tanks, "...which have the same design, structure, materials of construction and size" as depicted in the schematics above. Thus, at any given time in the study, at most eight (8) animals could be exposed to the same exposure chamber atmosphere in each tank, presumably (not stated in the report) one tank for males and one for females in the same dose group. The report describes the logistical details of managing such design limitations as follows:

> "The breathing tank was used repeatedly by groups of mice at different doses. Between any two treatment sessions, the breathing tank was washed and dried....The cleaning procedures include vacuum pump for 15 minutes, wet paper towel wiping, drying with paper towel and blowing with fan for 15 [minutes]....Furthermore, tank air was sampled and tested before the sprays of thymol, as well as after the sprays of thymol and after washing/cleaning of the tank....As a result, no trace of thymol was detected at the baseline (before the spray), and there was no detectable thymol left in the air in the tank, after exposure to the test articles....This confirmed that there is no carry-over of thymol between different treatment sessions."

Such procedures would have to have been completed after each exposure session for each of the four dose groups on each of the three weekly treatment sessions, just to manage the first of the two 6-month studies. The Sponsor does not describe how these logistical details were managed during the time that both 6-month studies were ongoing concurrently.

Importantly, as illustrated by the Sponsor's Figures 2 and 3 above, the exposure chamber was a closed system in which a single test article MDI was discharged into the chamber and the only exhaust was via the inhalation and exhalation of the eight animals being exposed at any given treatment session. There was no continuous airflow through the exposure chamber and there was no mechanism for monitoring and maintaining uniform oxygen and carbon dioxide concentrations or humidity in the chamber.

Most notably, there was no air sampling port on the chambers to allow for assessment of exposure chamber thymol concentrations or of aerodynamic particle size distribution (APSD) patterns concurrent with animal exposure. In fact, the report submitted initially with the NDA resubmission package did not provide any APSD data on the exposure chamber aerosols. An IR was sent to the sponsor requesting APSD data, as described below (see Test Article Characterization).

Animal Exposure

"At each treatment session, 15 sprays of test article were delivered into the tank following the procedures for actuation described in the E004 package insert. The stirring fan was set at 400 RPM and was started before the first spray of the test articles. Thirty (30) seconds after the last spray (t = 0 min), eight (8) mice in the restraints were immediately mounted to the breathing tank, and were required to inhale the air from the tank for 10 minutes. Mice were returned to their cage after each treatment." It should be noted that product usage instructions included in the package insert clearly state that the MDI drug product should be shaken prior to each actuation.

Test Article Characterization

The Sponsor asserts that actuation of the thymol-containing HFA MDI devices into the animal exposure chambers results in release of "...the thymol from each spray, (b) (4) Of note, thymol is a crystalline solid at room temperature with a melting point of approximately 51 °C and a boiling point of approximately 233 °C (https://pubchem.ncbi.nlm.nih.gov/compound/thymol). CMC review indicates that the (b) (4)

The physical state of thymol was not characterized in the original NDA resubmission to support the Sponsor's statement above (b) (4) Consequently, an IR was sent to the Sponsor requesting APSD data. The Sponsor submitted a 5-page summary document (SDN-48, received 31 August 2016) describing post-hoc experiments with the low- and high-dose thymol MDI test articles to assess particle sizing of thymol via Andersen cascade impactor and subsequent HPLC analyses. These data are summarized in the Sponsor's Table 2 below.

Table 2. PSD Study Results for Test Article-1 and Test Article-2

PSD Stages		Analytical Results*, mcg per spray					
Stage #	Cut Off Value (µm)	Article-1: Lot PL000314 (Thymol: (b) (4)% (b) (4) times of E004) (Net Delivery: (b) (4) mcg/spray)			Article-2: Lot PL00414 (Thymol: (b) (4)%, (b) (4) times of E004) (Net Delivery: (b) (4) mcg/spray)		
		Test 1	Test 2	Test 3	Test 1	Test 2	Test 3
The Individual Cascade Impactor Data (LoQ = 0.4 mcg)							
Valve	-	0.6	0.6	0.5	4.2	4.0	3.0
Actuator	-	6.3	4.7	4.6	10.2	8.3	9.3
IP/Head	-	<LoQ*	<LoQ	< LoQ	1.3	1.3	<LoQ
Stage 0	9	<LoQ	<LoQ	< LoQ	<LoQ	<LoQ	<LoQ
Stage 1	5.8	<LoQ	<LoQ	< LoQ	<LoQ	<LoQ	<LoQ
Stage 2	4.7	<LoQ	<LoQ	< LoQ	<LoQ	<LoQ	<LoQ
Stage 3	3.3	<LoQ	<LoQ	< LoQ	<LoQ	<LoQ	<LoQ
Stage 4	2.1	<LoQ	<LoQ	< LoQ	<LoQ	<LoQ	<LoQ
Stage 5	1.1	<LoQ	<LoQ	< LoQ	<LoQ	<LoQ	<LoQ
Stage 6	0.7	<LoQ	<LoQ	< LoQ	<LoQ	<LoQ	<LoQ
Stage 7	0.4	<LoQ	<LoQ	< LoQ	<LoQ	<LoQ	<LoQ
Stage F	< 0.4	0.4	0.4	0.5	3.9	4.1	6.6
Summary and Grouping Analysis							
Sum P1-5		<LoQ	<LoQ	<LoQ	<LoQ	<LoQ	<LoQ
Sum P3-4		<LoQ	<LoQ	<LoQ	<LoQ	<LoQ	<LoQ
Net Thymol Delivered (out of Actuator)		0.4	0.4	0.5	5.2	5.5	6.6
% Net Recovery		0.8%	1.0%	1.1%	2.3%	2.4%	2.9%
Particle Size Distribution Evaluation							
Mass Median Aerodynamic Diameter (MMAD, µm		N/A**	N/A**	N/A**	N/A**	N/A**	N/A**
Geometric Standard Deviations (GSD)		N/A**	N/A**	N/A**	N/A**	N/A**	N/A**

* < LoQ -- less than the limit of quantification, 0.4 mcg.
** N.A. -- not applicable

The Sponsor concludes from these analyses that (b) (4)

They further hypothesize that (b) (4) are due to the fact that (b) (4)

- (b) (4)
- (b) (4)

A second IR was sent to the Sponsor on 4 November 2016 that included the following additional requests for characterization of the test article with respect to its physical state:

a) "What is the amount of thymol present in each dose dispensed from your inhaler? Provide data to support the same. You may choose to use your validated thymol assay to measure the amount of thymol dispensed in 10 to 20 doses.
b) [redacted] (b) (4) Provide the amount of [redacted] (b) (4) thymol present in the dose dispensed from each actuation of your inhaler.
c) Indicate how this information relates to the amount and state of the thymol that mice received in your 6 month nonclinical studies with thymol. In your justification of the dose received, address the amount of thymol lost in the apparatus (57% to 71%). We note in your response to the Information Request sent on 8/25/16 that no particles were detected and the recovery rate was 0.8 to 2.9% using an Andersen Cascade Impactor."

The Sponsor's response was received on 9 November 2016. In addition to repeating previous assertions regarding their inability to detect particulate thymol during APSD analyses with an ACI, the submission summarizes the conduct of additional experiments designed to address the dose content uniformity (DCU) of thymol delivered from their MDI device. These data are summarized in the Sponsor's Table 1 below.

(b) (4)

Briefly, their DCU-1 method i (b) (4)

The DCU-2 method is an adaptation of the first method (b) (4)

The solvent is then quantitatively analyzed for thymol. Importantly, DCU-1 data reflect thymol levels "out of actuator," whereas DCU-2 data reflects thymol measured "out of valve."

The Sponsor concludes from these findings that "...the E004 device can quantitatively deliver all thymol out of the valve in the device" (b) (4) However, as to how these data impact on interpretation of their previous assertions that between 57 and 71 percent of thymol discharged into the animal exposure chambers (b) (4) the Sponsor states

only that they continue to “believe” that to be the case, without provision of any additional supportive data.

Observations and Results

Mortality

Number of surviving animals per cage (housed 4/cage) recorded weekly. All animals survived to study termination.

Clinical Signs

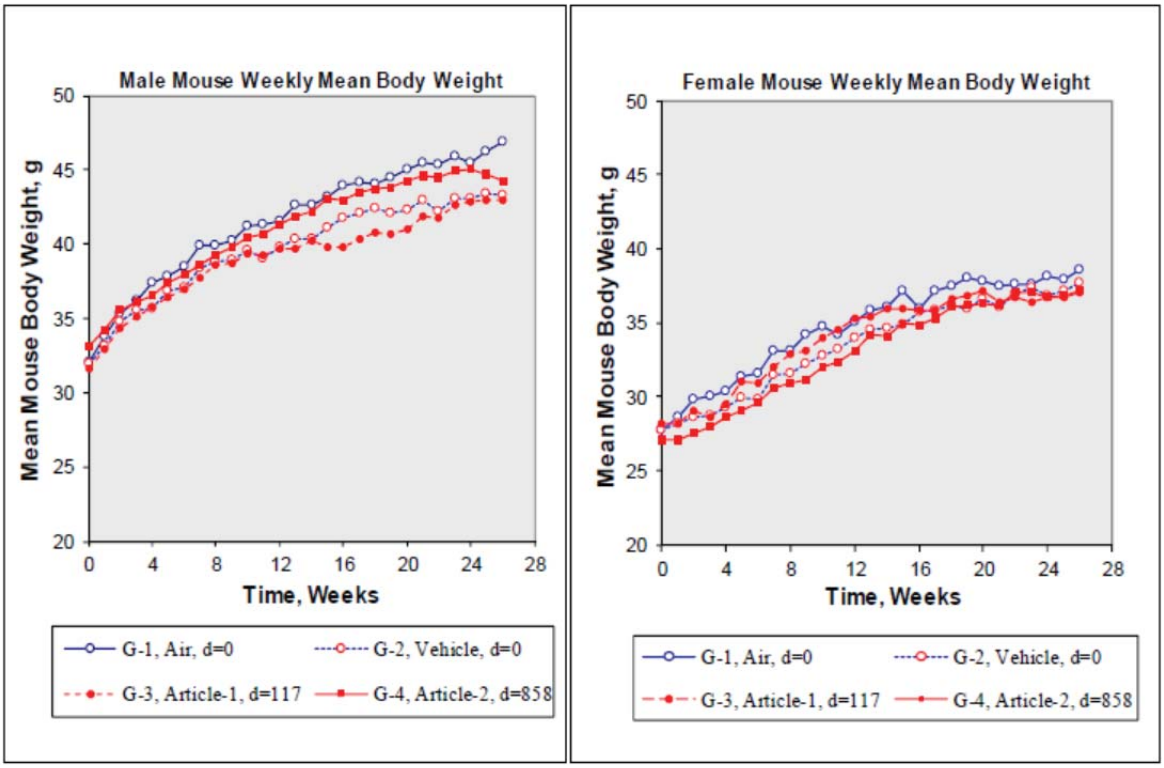
The “general appearance and functional behaviors of study animals” were assessed and recorded once weekly. The report states that the following items were assessed: “(i) Central nervous system, (ii) Autonomic, (iii) Respiratory, (iv) Circulatory, (v) Gastrointestinal, (vi) Genitourinary, (vii) Skin/Fur, (viii) Mucus Membrane, (ix) Eye, (x) Feces, and (xi) Urine.” However, neither the method(s) nor the timing of observations was described and observations were only reported as a single, apparently composite rating based on the following qualitative scale: “0 - appears normal; 1 - slightly abnormal; 2 - moderately abnormal; 3 - severely abnormal.”

No animal in either 6-month study was reported at any evaluation time point as having a rating score of anything other than zero (0). During the nonclinical inspection by OSIS, it was discovered that the Sponsor predetermined at the time of observation and recording that observed findings were not test article-related (discussion with Dr. Zhou Chen, OSIS).

Body Weights

Recorded weekly. Results are summarized in the Sponsor’s plots (Figure 5) of mean body weight for males and females below. Under the conditions of the study, there was no apparent correlation between thymol exposure and body weight effects.

Figure 5 Mean Body Weight Over 26-Week Study Period



Feed Consumption

Recorded per cage qualitatively ("normal" or "abnormal") once weekly. No effect on food consumption could be attributed to thymol exposure under the conditions of the study.

Ophthalmoscopy

Not performed.

ECG

Not performed.

Hematology

Not performed.

Clinical Chemistry

Not performed.

Urinalysis

Not performed.

Gross Pathology

Terminal procedures were not described in the report other than as excerpted below. The exact dates of necropsy were not provided in the report.

> "After the last treatment, the mice were sacrificed, and four (4) organs, including (i) lungs, (ii) bronchial lymph nodes, (iii) nasal passages/nasopharynx, and (iv) trachea, were taken out and preserved in a labeled histology container prefilled with 10% Neutral Buffered Formalin. The organs were sent to (b) (4) for histopathologic evaluation. The organs from Set-1(Study 1) were sent to (b) (4) and those for Set-2 (Study 2) on (b) (4)

Gross necropsy observations were not reported other than that for a single Group 4 female (#174-08F3) discussed in the Study Pathologist's Necropsy-Microscopy Correlation Table (Attachment 3). This states that a "single pinpoint white raised area" on the right apical lung lobe ("noted at gross trimming") correlated with microscopic findings of alveolar focal subpleural macrophages, minimal.

Organ Weights

Not collected.

Histopathology

Adequate Battery: This was a targeted study, directed at specifically assessing the potential toxicity of inhaled thymol to locally exposed tissues. As such, the organ tissues examined are considered to be adequate.

Peer Review: Not performed.

Histological Findings: A signed and dated Study Pathologist's report was included in the submission. According to the Study Pathologist's report, "Hematoxylin and eosin-stained (H&E) slides of lung lobes, trachea, four levels of the nasal turbinates, and bronchial lymph node were prepared by (b) (4) for microscopic evaluation by a board-certified veterinary pathologist."

Under the conditions of the study, microscopic examination of the selected respiratory system tissues revealed no evidence of effects that could be directly attributed to exposure to thymol.

Special Evaluation

None.

Toxicokinetics

Blood sampling for assessment of actual plasma thymol concentrations was not performed on any of the toxicity study animals. Rather, a separate PK study in CD-1 male mice was conducted in May, 2016, under separate protocol (E004-VO-005). Mice were randomized into one of two treatment groups (16 mice/group). The first group received under isoflurane anesthesia a single intravenous (IV) injection of thymol (b) (4)

mg/mL in saline, dose volume 0.16 mL, or approximately 0.48 mg/kg). The second group was administered a single 10-minute inhalation exposure to thymol (b) (4)% in HFA MDI) via the same exposure chamber and parameters as employed in the earlier toxicity studies. Blood was collected via retro-orbital sinus under isoflurane anesthesia pre-dose and at 2, 5, 10, 20, 30, and 60 minutes following completion of dosing. Results are summarized in the Sponsor's Table 20 and Figure 6 below. Estimated TK parameters are provided in the Sponsor's Table 22 below.

Table 20 Thymol PK Parameters by IV Injection or Inhalation in Mouse Model

Delivery Route	IV	"Inhalation"
Species	Mouse	Mouse
Delivery Method	0.16 mL of (b) (4)mg/mL of Thymol	15 Sprays of (b) (4)% Thymol into 21.5L Tank, Breathing for 10 min
Dose, mcg/treatment	16	15.5*
Dose, mg/kg mouse	0.48	0.47
# of mice treated	8X2	8X2
PK Time Points	Mean Concentrations (ng/mL)	
0 minutes	0.0	0.0
2 minutes	76.6	39.2
5 minutes	41.4	19.2
10 minutes	13.6	16.0
20 minutes	3.7	6.9
30 minutes	2.6	6.4
60 minutes	0.2	3.9

* see Table 8.

Figure 6 PK Curves of Thymol in Mouse Serum

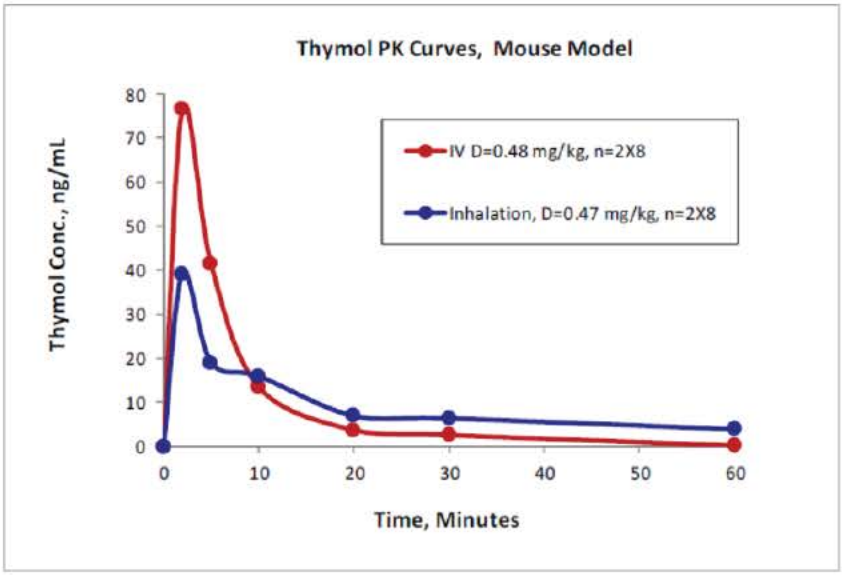


Table 22 Estimated PK Parameters for Thymol Mouse Model: Inhalation and IV

Route of Administration	IV Injection	Inhalation (inh)	Ratio of Inhalation to IV
Treatment			
# of mice treated	8X2	8X2	-
Dose, mcg/treatment	16	15.5*	98%
Dose, mg/kg mouse	0.48	0.47	98%
PK Parameters			
C_{max}, ng/mL	77	36	47%
$AUC_{0\text{-}60min}$, ng/mL×min	551	324	59%
t_{max}, min	2	2	100%
$t_{1/2}$, min	3.9	3.9	100%

* See Table 8.

The Sponsor also conducted additional PK analyses following exposure of mice inserted into the exposure chambers tail first (see Sponsor's Figure 7 below) to assess the potential of thymol systemic absorption via the fur/skin. The Sponsor describes these experiments as "...outside of the original protocol" and for investigational purposes only.

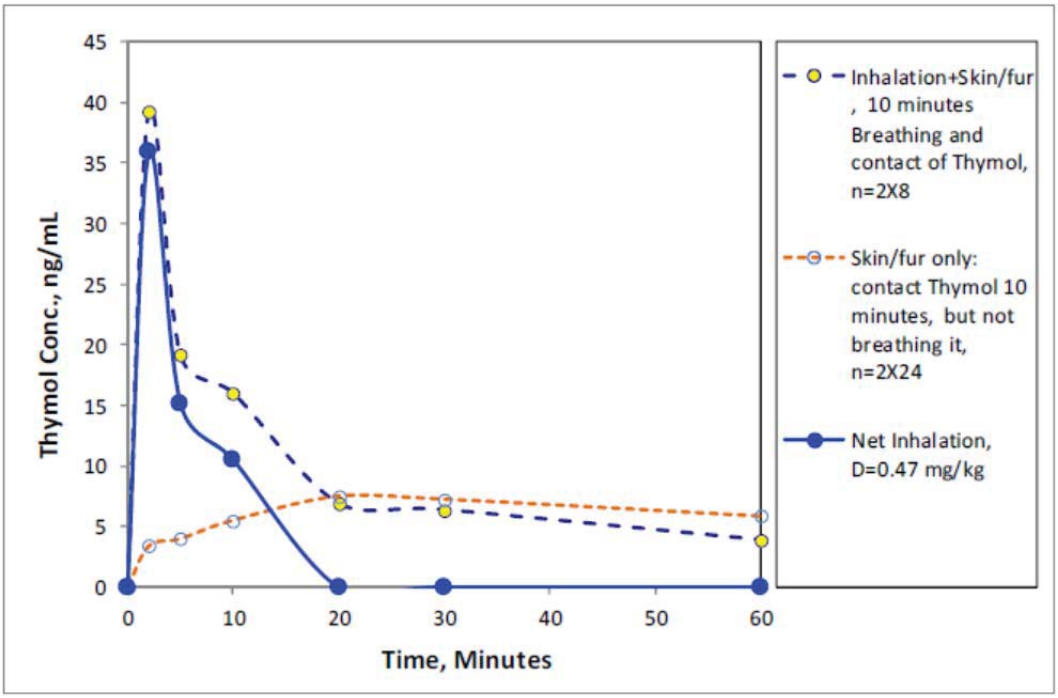
Figure 7 Position of Mice for Determination of Thymol through Skin Absorption

A total of 48 mice were exposed in this manner due to "highly fluctuating" data, which are summarized in the Sponsor's Table 21 and Figure 8 below.

Table 21 Net Inhalation Thymol Concentration (ng/mL) in Mouse Serum

#	Time, minutes	IV, D=16 mcg		"Inhalation", D=15.5 mcg			
		Experimental Data	Model, Eq. (15)	Experimental Data			Model, Eq. (15)
				"Inhalation" Including Hair/skin Absorption	Skin Only	Net Inhalation	
1	0	0.0	0.0	0.0	0.0	0.0	0.0
2	2	76.6	73.6	39.2	3.4	35.9	36.6
3	5	41.4	46.1	19.2	4.0	15.1	28.6
4	10	13.6	18.8	16.0	5.5	10.5	12.2
5	20	3.7	3.1	6.9	7.5	0.0	2.0
6	30	2.6	0.5	6.4	7.3	0.0	0.3
7	60	0.2	0.0	3.9	5.9	0.0	0.0

Figure 8 Thymol Mouse PK Curve for Net Inhalation



Dosing Analysis

The report includes only a single set of tank air sampling data, which suggests (not specifically acknowledged in the report) that the only such sampling performed was during the single set of thymol concentration determination experiments performed sometime other than during actual animal exposure sessions (see below). Therefore, it

cannot be determined from the report whether cross-contamination may have occurred across dose groups over the course of the 6-month study duration.

The Sponsor's efforts at measuring the air thymol concentration (using LC-MS/MS) in the exposure chambers were carried out in separate experiments (actual dates not reported), wherein 7 out of the 8 animal exposure ports were blocked and an air sampling tube was connected to the 8th port. Thirty seconds after the last spray, the air sampling pump was run for 10 minutes at 100 mL/min. "The actual concentration of thymol in the tank sampled during 0-10 min after 15 sprays of test articles, which is the average thymol concentration in the breathing tank during the 10 minutes of study period for each treatment, was measured from three (3) replicates. Between measurements of each replicate, a method blank was also performed to assure the data quality." Results are summarized in the Sponsor's Table 5 below. Notable is the Sponsor's estimation that 57% to 71% of the thymol (b) (4)

Table 5 Determination of Actual Thymol Concentrations in the Tank

Test Article	Thymol/ spray mcg	Tank size, L	Test #	# of Spray	Thymol Amount/Concentration in the Breathing Tank			Actual Thymol Concentration in the Air of the Tank, (Sampling 10 minutes 0-10')				% of Thymol	
					Amount mcg	Theoretical Concentration*		Data, mcg/L	Mean ± SD mcg/L	CV	Mean ppm**	In the Air	Adsorbed by Inner Wall
						mcg/L	ppm**						
Article-1 Thymol (b) (4)	(b) (4)	21.5	1	15	687	32	5.2	8.69	9.27 ± 0.50	5%	1.5	29%	71%
			2	15	687	32	5.2	9.51					
			3	15	687	32	5.2	9.60					
Article-2 Thymol (b) (4)		21.5	1	15	3,434	160	26.0	71.1	69.0 ± 2.0	3%	11.2	43%	57%
			2	15	3,434	160	26.0	67.2					
			3	15	3,434	160	26.0	68.7					

* Theoretically, assuming there is no adsorption by the inner wall of the breathing tank.
** parts per million, as volume to volume.

Subsequent to receipt of comments from the Agency, the Sponsor conducted an additional experiment to measure exposure chamber thymol concentration at different time points, using a sampling pump rate of 500 mL/min and a one-minute sampling time. Sampling occurred at 0, 10, and 20 minutes after the last of 15 sprays. These results are summarized in the Sponsor's Table 6 below. These data indicate that exposure chamber thymol concentration declined by 25% and 52% at the low ((b) (4) %) and high ((b) (4) %) thymol MDI concentrations, respectively, between the T = 0 and T = 20 min time points.

Table 6 Thymol Concentrations in the Breathing Tank at Different Time Points

Test Article	Thymol/ spray mcg	Tank size, L	# of Spray	Total Thymol Amount in the Tank		Test #	Measured Data for time, mcg/L				Data for Sampling directly from 0 to 10', x_1	Δ% of x_2 vs. x_1
				mcg	mcg/L		0	10'	20'	0-10' per Eq. (5) x_2		
Article-1 Thymol (b) (4)%	(b) (4)	21.5	15	687	32	1	9.17	9.01	7.16	9.09		
			15	687	32	2	9.60	9.04	7.52	9.32		
			15	687	32	3	9.30	6.68	6.25	7.99		
						Mean	9.36	8.24	6.98	8.78	9.27	-5%
						SD	0.22	1.35	0.65	0.71		
						CV	2.3%	16.4%	9.4%	8.1%		
Article-2 Thymol (b) (4)%	(b) (4)	21.5	15	3434	160	1	81.68	49.90	36.66	65.79		
			15	3434	160	2	75.54	58.11	38.40	66.83		
			15	3434	160	3	61.35	57.99	30.59	59.67		
						Mean	72.86	55.33	35.21	63.89	69.01	-7%
						SD	10.43	4.71	4.10	3.87		
						CV	14.3%	8.5%	11.6%	6.1%		

In an IR sent on 4 November 2016, the Sponsor was requested to justify the differing flow rates used in sampling air from the exposure apparatus:

> "In your summary report, different flow rates were used when measuring thymol. Specifically, the air was initially sampled at 100 mL/min for 10 min (page 23 of your summary report). Additional measurements used a sample rate of 500 mL/min and a 1 min sampling time at 0, 10 and 20 min (page 26 of your summary report). Justify the use of the different sample rates, and how they are physiologically relevant to inhalation in rats."

The Sponsor's response (received 9 November 2016) stated that the air flow rates employed were necessary "...to sample sufficient air volume to analyze the thymol." The resulting consistency in thymol concentration values obtained between the two flow rates indicated that "...there was no impact on the average concentration determined by either sampling method" and "therefore...no impact on the calculated inhalation exposure from the air in the breathing tank inhaled by mice (calculated physiological exposure)."

11 Integrated Summary and Safety Evaluation

NDA 205920 seeks approval of an epinephrine HFA MDI for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older in the OTC setting. The proposed HFA MDI drug product is the result of reformulation of an earlier marketed product with a CFC propellant.

The current submission constitutes the Sponsor's resubmission of the application following a CR action by DNDP in which a primary deficiency identified was a lack of nonclinical safety support for the proposed formulation excipient, thymol, under chronic inhalation conditions of use. The CR letter stipulated that this deficiency be addressed by submission of a 6-month repeated dose inhalation toxicity study in an appropriate nonclinical species.

Included in the current submission is a single, summary report of two 6-month repeated dose inhalation toxicity studies in CD-1 mice. The two studies were initiated approximately three weeks apart, but were otherwise identical and conducted in parallel. Also included in the summary report are results of a separate TK analysis in mice under comparable exposure conditions but conducted approximately 1.5 years later. A study protocol for the inhalation toxicity study was submitted to DNDP for comment but not until approximately 2-3 months after both studies had been initiated. An IR was sent to the Sponsor on 4 November 2016 that included a request for the individual study reports for each of the three conducted studies. The response received on 9 November 2016 indicates that separate reports do not appear to exist for the two 6-month toxicity studies, as the decision to merge these two studies occurred while the two studies were still ongoing. Refer to the final OSIS GLP inspection report as to whether appropriate protocol amendments documenting this decision were identified. A separate PK study report (23 pages) was included in the IR response and these data appear to be consistent with those submitted in the original NDA resubmission.

On face, the study data provided suggest an absence of either local or systemic adverse effects in mice following repeated inhalation exposure for six months. However, as outlined above, the study design employed suffers from a number of significant deficiencies based on review of published literature and national and international nonclinical testing guidelines.[1] These deficiencies include the following:

- Exposure chamber aerosols were not continuously generated throughout duration of animal exposures.
- No concurrent and repeated assessment of exposure chamber concentrations.
- No concurrent and repeated assessment of exposure aerosol APSD.
- No continuous airflow through the exposure chambers; humidity and oxygen concentration were not monitored and reported.

[1] Tepper et al. (2016) Int J Toxicol 35:376-92. OECD (2009), Test Guideline No. 413: Subchronic Inhalation Toxicity: 90-day Study, OECD Publishing, Paris. US EPA (1998), Health Effects Test Guidelines OPPTS 870.3465: 90-Day Inhalation Toxicity, EPA 712–C–98–204. Wolff and Dorato (1993) Crit Rev Toxicol 23:4, 343-369.

- Exposure duration of 10 minutes/day, 3 days/week is less than the maximum feasible duration and frequency.
- Number of animals (8/sex/group) is less than optimal.
- Respiratory parameters including respiratory rate, minute volume and tidal volume were not measured.
- Blood gas parameters pO_2 and pCO_2 were not measured. Blood pH was not measured.

Due to the lack of concurrent sampling of the chamber air for thymol during animal exposure, it was difficult to determine if animals were being exposed to a concentration of thymol higher than the clinical formulation (b) (4) % thymol). The air was sampled at 100 mL/min for 10 min, or at 500 mL/min for 1 min at 1, 10, and 20 min after thymol was discharged into the exposure chamber. The Sponsor justified the high rate of sampling in the IR response received on 9 November 2016 by stating that the air samples were meant to capture a snapshot of the thymol contained in the tank. The samples show that there was thymol in the tank, but it is difficult to determine the concentration the animals were exposed to in the breathing zone based on these data.

Importantly, the Sponsor's air sampling showed that there was a loss of 57% to 71% of the nominal dose of thymol. The Sponsor proposed (b) (4) However, this proposal was not supported with data (b) (4) Other possible explanations are that the amount of thymol expelled from the MDI was significantly lower than the nominal dose or that the Sponsor's assay for thymol was not accurate.

To address these concerns, FDA requested data characterizing the physical state of thymol in the chamber, the amount of thymol discharged from the MDI, and the Sponsor's assay for thymol discharged from the MDI. On 25 August 2016, FDA sent an IR to the Sponsor asking for particle size distribution and recovery using an Andersen Cascade Impactor. The Sponsor provided data showing that recovery rate was 0.8% to 2.9% for particulate thymol, (b) (4) This appeared to support the Sponsor's assumption that (b) (4)

On 4 November 2016, the Sponsor was asked to characterize the amount and physical state of the thymol discharged from the MDI. The Sponsor provided further data on 9 November 2016, using MDI formulations with (b) (4) % thymol. The analytical methods and results in the study titled "Final Report for The Amount of Thymol per Actuation Studies" (study # QARD-029-16-00FR) were assessed by CMC reviewer Dr. Muthu Ramaswamy and determined to be reasonable (verbal communication, 9 November 2016). The study had two parts, designated DCU-1 and DCU-2. Study DCU-2 showed that the amount of thymol discharged from the MDI was within acceptable

range using the dose content uniformity method (based on USP <601>). Importantly, this showed for the first time that the Sponsor could recover the expected amount of thymol expelled from their MDI when spraying the formulations used in the nonclinical study.

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

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

In assessing the overall safety of the proposed level of (b) (4)% thymol, the limited amount of thymol exposure expected (approximately (b) (4)µg/day) and the previous human experience with thymol were taken into consideration. Future proposed products with higher levels of thymol exposure should be supported by more robust inhalation data with thymol.

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

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/s/

DONALD C THOMPSON
11/16/2016

JANE J SOHN
11/16/2016
I concur.

Chronic Toxicity of Thymol on Lung and Respiratory Tract

AMPHASTAR PHARMACEUTICALS, INC.

Protocol No. E004-VO-002

IND 074,286 (serial 082);

NDA 205-920

In the original NDA review, thymol (2-isopropyl-5-methylphenol), [redacted] in the proposed formulation for epinephrine inhalation aerosol (E004), was considered a novel excipient for the sought route of administration (inhalation) because its safe use via inhalation has not been documented in CDER-approved drug products. In the Complete Response letter to the sponsor dated 5/22/2014, the Agency asked the sponsor to provide safety information for the chronic exposure to thymol via inhalation. This memo serves as a review for the 6-month inhalation toxicity study which is designed to assess the chronic safety of the lung and respiratory tract in mice, when exposed for six months to two concentrations of thymol [redacted]%, representing [redacted]% thymol content in E004). Mice will be exposed to the vehicle or to E004 containing thymol by the inhalation route three (3) times each week for six (6) months.

The clinical E004 formulation and the thymol-enriched formulation are shown in table 1 below:

Table 1. Ingredients of E004 and Study Articles

Study Article	Name	Material	Percent (w/w)
	E004	Epinephrine Polysorbate 80 Ethanol **Thymol** HFA-134a	[redacted]
Vehicle Control		Epinephrine Polysorbate 80 Ethanol Thymol HFA-134a	
Article 1	[redacted] X Thymol	Epinephrine Polysorbate 80 Ethanol **Thymol** HFA-134a	
Article 2	[redacted] X Thymol	Epinephrine Polysorbate 80 Ethanol **Thymol** HFA-134a	

Study Design and Procedures

The solution is sprayed into the breathing tank where up to 4 mice can be attached on each side of the tank (see picture of the tank, figure 1). The number of sprays determines the amount of thymol available in the tank. With the stirring fan set at 400 RPM and 30 seconds after the last spray (t = 0 min), the mice are mounted to the inhalation chamber to breath for 10-minutes in each session. Mice are returned to their cages after each session. There will be three sessions each week and the whole study will last approximately 6 months. The goal is that by the end of the study, each mouse would be exposed to a maximum of seventy-two sessions, 10-minute each.

(b) (4)

The concentration of thymol in the air will be determined using an Amphastar LC-MS protocol where concentrations will be sampled on three separate occasions.

Mice will be monitored for general health conditions regularly during the study.
At the end of the study, the following organs will be evaluated histopathalogically: lung, nasal passages/nasopharynx, trachea, bronchial lymph nodes. The histopathology assessment will be conducted by an independent laboratory (b) (4)

The study will include four treatment groups using 8 animals/sex/group where mice will be exposed to four different treatment groups (control room air, Vehicle Control, (b) (4) test articles) consisting of fifteen sprays each (see Table below).

No.	Number of Sprays for Thymol HFA			Theoreticle Thymol in Tank (21L)		Measured Thymol in Tank	Mice Breathing Time (min)	Mice Breath Rate mL/min	Assumed Deposition Rate	Net Thymol Dose for Mice		Thymol in Mice Lung[2], mcg/g	Comparative Human Dose	# of Mice
	Room Air	Vehicle	(b) (4)	mcg	mcg/L	mcg/L				mcg	mcg/kg			
1	√			0	0.0		10	22.5	-	-	-	-	-	8M+8F
2		15		0	0.0	[1]	10	22.5	-	-	-	-	-	8M+8F
3			15	690	32.9	[1]	10	22.5	50%	3.70	148	18.5	200X	8M+8F
4			15	3450	164 3		10	22.5	50%	18.48	739	92.4	1000X	8M+8F

[1]: To be determined experimentally. Approxmately 20% of theoretical value. [2]: Based on theoreticle thymol concentration in tank.

Protocol assessment

- The protocol did not describe in detail the sampling times for thymol; it is recommended that sampling be done before and after exposure to the test article. It is also suggested to include measurements of the negative control group.
- Measurement of the test article in the blood (toxicokinetic measurement), if possible, should be done for treated animals to verify that they received the intended treatment exposure.

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/s/

WAFA HARROUK
04/03/2015

PAUL C BROWN
04/07/2015

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW ADDENDUM

Application number:	205-920
Supporting document/s:	S0034
Applicant's letter date:	May 12, 2014
Product:	Epinephrine inhalation aerosol (HFA MDI, 125 µg per inhalation)
Indication:	"For the temporary relief of mild symptoms of intermittent asthma in adults and children ≥12 years of age or older"
Applicant:	Armstrong Pharmaceuticals, Inc., a subsidiary of Amphastar Pharmaceuticals
Review Division:	DNCE
Primary Reviewer:	Wafa Harrouk, Ph.D.
Secondary Reviewer:	Paul Brown, Ph.D.
Division Director:	Theresa Michele, M.D.
Project Manager:	Daniel Reed, MPH

Background

Epinephrine HFA MDI is being considered as a replacement for the Primatene Mist which was removed from the market to eliminate CFC-containing products. The indication sought is for the "temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older", which would be considered a chronic indication. In addition to switching propellants, other changes to the formulation have been made including the addition of thymol (b) (4) The use of thymol in inhalation products indicated for chronic use has not been documented. The sponsor was asked in an "information request" letter dated May 9th, 2014 to provide nonclinical information supporting the safety of chronic inhalation of thymol in this formulation.

The sponsor responded on May 12th, 2014 with the following arguments in support of the safe use of thymol:

1. Thymol is consumed by humans through the diet and for this reason, from a dietary exposure standpoint, has been determined to have relatively low toxicity. (b) (4)

2. (b) (4) The sponsor argues that since E004 (b) (4) "would not add any significant risk" to safety.

3. Exposure amount for thymol from E004 per day and per week were provided. The formulation of E004 includes (b) (4) % of API (epinephrine free base) and (b) (4) % of thymol. The label claim for E004 is 125 µg/inhalation of epinephrine with an expected exposure to thymol calculated at (b) (4) µg/inh((b) (4)). Assuming that the consumer will

use 8 inhalations of E004 per day, the exposure amount for thymol per day is calculated at (b)(4) µg /day: [(8 inh /day) x (b)(4) µg/ inh)].

The sponsor further argues that under the standard definition of "intermittent asthma," the consumer may use E004 twice a week, with a maximum weekly exposure to thymol from E004 of (b)(4) µg/week.

4. Prior human experience from the use of Inhaled thymol in Halothane, prior to its withdrawal from the market, was cited.

5. Karvol inhalation capsules which consists of 6 APIs, including 3.15mg thymol/capsule (Reckitt Benckiser Healthcare, UK) was also cited. The sponsor provided an assessment of adverse events possibly related to thymol based on the electronic Medicines Compendium (eMC, www.medicines.org.uk) from the use of Karvol Inhalant Capsules. This product has also been discontinued.

Conclusions and Recommendations:

To support the safe use of thymol via the inhalation route for a chronic duration, the sponsor cited the extensive oral use of thymol and the use via inhalation of two products, Halothane and Karvol Inhalation Capsules. Because the safety of oral exposure to thymol has been well documented, the request in the IR letter specifically focused on chronic data obtained via the inhalation route. The sponsor did not submit data in support of the chronic use of thymol via the inhalation route. Halothane was for acute use. Thymol has not been considered GRASE as an active ingredient for OTC use for any indication including nasal decongestants (21 CFR 310.545(a)(6)(ii)(A)). In addition, the use of thymol in Halothane and Karvol Inhalation Capsules has been discontinued and an adequate adverse event analysis cannot be conducted to assure the long term safe use of thymol as proposed for this indication. In conclusion, the information provided in the letter dated May 12, 2014 does not provide any additional data that can be used to support the chronic exposure to thymol via inhalation. Nonclinical information should be provided to support the safety of chronic inhalation of thymol. As noted in the

recommendation provided in the primary Pharm/Tox review, a repeated dose inhalation toxicity study of 6 months duration in an appropriate species that shows no adverse findings could support the use of thymol in this formulation.

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/s/

WAFA HARROUK
05/20/2014

PAUL C BROWN
05/20/2014

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	205-920
Supporting document/s:	S000
Applicant's letter date:	July 17, 2013
CDER stamp date:	July 22, 2013 (eCTD format)
Product:	Epinephrine inhalation aerosol (HFA MDI, 125 µg per inhalation)
Indication:	"For the temporary relief of mild symptoms of intermittent asthma in adults and children ≥12 years of age or older"
Applicant:	Armstrong Pharmaceuticals, Inc., a subsidiary of Amphastar Pharmaceuticals
Review Division:	DNCE
Primary Reviewer:	Wafa Harrouk, Ph.D.
Secondary Reviewer:	Paul Brown, Ph.D.
Division Director:	Theresa Michele, M.D.
Project Manager:	Daniel Reed, MPH

Disclaimer
Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205-920 are owned by Armstrong Pharmaceuticals, a subsidiary of Amphastar Inc., for which the above mentioned sponsor has obtained a written right of reference.
Any information or data necessary for approval of NDA 205-920 that the sponsor does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are included for descriptive purposes only and are not relied upon for approval of NDA 205-920.

Executive Summary

Epinephrine HFA-metered dose inhaler (MDI), a proposed replacement for epinephrine chlorofluorocarbon (CFC) -MDI, is an inhaler indicated for the "temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older". The sponsor is switching from the propellant CFC to HFA due to the phase-out of the use of products containing CFC per the Montreal Protocol[1]. In addition to switching propellants, other changes to the formulation have been made including the addition of thymol (b) (4) The application did not include any nonclinical data. Letters of authorization were provided for the active ingredient, (b) (4)

Recommendations

Approvability: The nonclinical information submitted does not fully support the safety of the formulation. In particular, there are no nonclinical data to support the safety of chronic inhalation of thymol. In the absence of adequate clinical safety data to support the chronic use of inhaled thymol, the application is considered not-approvable from the Pharmacology/Toxicology perspective.

Comments to be added to the C/R letter:

The use of thymol in inhalation products indicated for chronic use has not been documented. Therefore, you will need to provide nonclinical information supporting the safety of chronic inhalation of thymol. If such information is not currently available, a repeated dose inhalation toxicity study of 6 months duration in an appropriate species that shows no adverse findings could support the use of thymol in your product.

[1] FDA News Release, September 22, 2011, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm272872.htm,

Overview & Regulatory History

Armstrong Pharmaceuticals (Armstrong), has submitted a New Drug Application (NDA 205-920) to the Division of Nonprescription Clinical Evaluation (DNCE) for epinephrine HFA-MDI, also referred to in this document as E004. The proposed indication is the "temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older".

E004 is proposed as a replacement for epinephrine CFC-MDI, for over-the-counter (OTC) use, which has been phased out of the market place since December 31, 2011, in an effort to decrease the emissions caused by the ozone-depleting CFCs as outlined by the Montreal Protocol. The innovator product, Primatene® Mist (NDA 16-126, Wyeth) was approved in 1967. A generic version of epinephrine CFC-MDI (ANDA 87-997, Armstrong) was approved in 1984. Armstrong purchased the Primatene® Mist trademark from Wyeth and the product has been discontinued from distribution and the associated NDA (016-126) was withdrawn. Until Dec 31, 2011, the epinephrine CFC-MDI was marketed as a 220 µg/inhalation formulation, and was indicated as a bronchodilator for the "temporary relief of occasional symptoms of mild asthma: wheezing, tightness of chest, shortness of breath" in adults and children ≥4 years of age and older.

The initial development program for E004 was initiated with DNCE on March 27, 2007 under IND 74,286. An NDA (204-496) was submitted in May 2013, but was not successfully filed due mainly to several electronic submission- related deficiencies. The same product was resubmitted on July 22, 2014 under NDA 205-920 which was filed successfully and is the subject of this review.

Of note in this NDA is the name of this product; the sponsor had proposed the name [redacted] (b) (4) However, because there are a number of product differences between the former Primatene Mist and the current one, the Primatene name was not accepted by the Agency. The DMEPA review team argued that the proposed name implies that the new product is an updated version of the old product, Primatene Mist. However, since the new product has different dosing instructions and different features (such as

the dose counter, which if approved would be the only metered dose inhaler available OTC) from the previous product, using the same name may impact the safe and effective use of this inhaled product which needs to be fully recognized and understood on its own by consumers. No decision has been made regarding the name of this product at the time of completion of this review.

Drug Information

Relevant INDs, NDAs, BLAs and DMFs

- IND 74, 286
- Primatene® Mist reference listed product (RLD), under Wyeth's NDA 16-126, approved on November 08, 1967. Armstrong's Epinephrine Inhalation Aerosol USP, ANDA 87-907, approved on May 23, 1984. Since the innovator drug is no longer available, Amphastar used Armstrong's generic Epinephrine CFC-MDI, manufactured under ANDA 87-907 as the active control drug in Epinephrine HFA MDI clinical studies where an active control is necessary.

- Letters of authorization (LOA) for the following DMFs were provided in the submission:
  - DMF # (b) (4)
  - DMF # (b) (4)

Additional DMF LOAs relevant to the CMC review were provided for the MDI components of the inhaler.

Drug Formulation: This is an orally inhaled epinephrine formulation with 1-2 inhalation(s)/dose up to a maximum of 8 inhalations in 24 hour. The user has to wait at least 4 hours between doses. This product is likely to be used chronically due to the nature of the indication sought, asthma. The filling amount of each E004 MDI unit is (b) (4) g and about (b) (4) inhalation puffs (b) (4) mg/puff). Maximum daily dose of E004 is 8 inhalations per day per the E004 proposed label.

The formulation contains epinephrine as the active ingredient (a stimulant of both α and β adrenergic receptors) in suspension in HFA-134a propellant. The proposed dose for E004 (2 × 125 mcg) is 43% lower than that for Primatene® Mist (2 × 220 mcg) due to a claim of higher delivery efficiency of the suspension formulation of E004. Inactive ingredients used for the suspension formulation include HFA-134a, ethanol, thymol and polysorbate 80. The epinephrine ingredient [redacted]

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

The list of inactive ingredients in the current application differs from that of the previously used Primatene Mist where the inactive ingredients used in the previously approved Primatene included: Ascorbic acid, dehydrated alcohol (34%), dichlorodifluoromethane (CFC 12), dichlorotetrafluoroethane (CFC 114), hydrochloric acid, nitric acid and purified water. The sponsor changed the formulation in this current NDA to a suspension which would require priming and cleaning on a regular basis due to product settling and potential clogging of the device by the suspension. It appears that device and dose indicator malfunctions were reported for this device more frequently than is usual for other marketed MDIs. This topic was recently discussed at an advisory meeting for this NDA (http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/ucm380890.htm).

Comments on Novel Excipients

No novel excipients were identified in this formulation. All excipients are listed in the FDA's inactive ingredient data base.

Polysorbate 80 is listed in the inactive ingredient data base as an excipient in a jet nebulizer for budesonide inhalation suspension (Pulmicort respules), which is approved for (b) (4) maintenance medication.
Dehydrated alcohol has been used at 10% in inhaled metered dose formulation for inhalation products.
Thymol ((b) (4)%) has been used in an inhaled product, Halothane, under ANDA 80810 (approval date May 9, 1972), (b) (4)
Halothane is indicated as an inhalational general anesthetic, prescribed for the induction and maintenance of general anesthesia which is considered a short term use. The use of thymol in inhalation products indicated for chronic use has not been documented. It should be noted that Halothane has been discontinued in the USA but is still available in other countries. It does not appear that this product was discontinued for safety reasons. No data were available for repeat dose toxicity studies for thymol via the inhalation route. Reproductive/developmental studies and carcinogenicity studies do not appear to be available for thymol.

Safety assessment of thymol: In order to assess the potential adverse effects of using thymol in this inhaled chronic product, a review of the literature was conducted. Thymol is used as an active ingredient in pesticide products at concentrations ranging from 0.027%-13%w/w. Thymol is registered for use as animal repellents, fungicides/ fungistats, medical disinfectants, tuberculocides, and virucides. In addition, thymol has many non-pesticidal uses, including use in perfumes, food flavorings, mouthwashes, pharmaceutical preparations and cosmetics. (b) (4)
A RED document was found for thymol which was published by the Environmental Protection Agency for its evaluation of thymol as an active ingredient as a pesticide as well as a number of published papers (see appendix 2 for more details).
The literature indicates the presence of several repeat dose general toxicity studies, several genotoxicity studies and a reproductive study in avian embryos. There does not

appear to be data available for repeat dose studies for thymol via the inhalation route, reproductive and developmental studies or carcinogenicity studies.

The (b) (4) percentage of thymol used (b) (4) %) in the proposed formulation should be taken into consideration when assessing its potential risk in this product.

The maximum amount of thymol inhaled daily from the product would be approximately (b) (4) µg. The maximum daily intake of thymol as a flavoring is estimated to be between 51-160 µg/person. This daily intake is not considered to represent a safety concern (JECFA evaluation, July 3, 2007). Therefore, the safety of thymol in the product from a systemic exposure perspective is supported. However, its safety from a chronic inhalation perspective is not supported by nonclinical data.

Comments on Impurities and Degradants of Concern

The sponsor has identified the following potential impurities, all of which are below the threshold of toxicological concern for impurities and degradants per ICH Q3B (R2).

Summary of Potential Impurities and Armstrong's Control Specifications of Primatene® HFA (E004)

Origin	Potential Impurities	(b) (4) Specifications		Method Used
Impurities from the API or degradants	(b) (4)	NMT NMT NMT NMT NMT	(b) (4)	(b) (4) High Performance Liquid Chromatography (HPLC)
	Largest Unknown Impurity	NMT		
	Total of all impurities	NMT		

Comments on Leachables from Container Closure System

The sponsor identified several leachables from the container closure system which have been added to the revised protocol for the post-approval stability program from the drug product. The filling amount of each E004 MDI unit is (b) (4) g and about (b) (4) inhalation

puffs (b) (4) mg/puff). Maximum daily dose of E004 is 8 inhalations per day per the E004 proposed label. Identified leachables were: (b) (4)

The sponsor provided justifications for the specifications set for each leachable which were provided by the MDI maker, (b) (4) (see sponsor's correspondence for an IR letter dated 3/25/2014), (b) (4)

This provides the theoretical maximum possible concentration of each leachable chemical in the drug product, from which the maximum human exposure level (MHEL) can be calculated.

Source	Extractable Compound	Extractable Spec (µg/g, ppm)	Maximum Leachable per Valve (µg)	Maximum Leachable in Product L_{max} (µg/g)	Maximum Leachable per inhalation I_{max} (µg/inh)	MHEL at the Maximum Propose Label D_{max} (µg/day)
(b) (4)						

*

Due to structure and source similarity, (b) (4) were evaluated together by the sponsor. The total (b) (4) is calculated at (b) (4) µg/day at the maximum E004 proposed labeled dose, and can be further calculated as (b) (4) µg/kg/day based on

70 kg human body weight. The sponsor provided a toxicological justification suggesting that this limit would be acceptable.[2]

[redacted] If the E004 proposed maximum labeled daily dose is used, [redacted] µg/day,respectively. The [redacted] of combined [redacted] µg/day, or [redacted] µg/kg/day (assuming a 70 kg human body weight). [redacted] used in FDA approved pharmaceutical products and medical devices. The [redacted] in E004 is calculated at [redacted] µg/day (or [redacted] µg/kg/day).

Three (3) batches of E004 drug product were analyzed for potential leachable compounds (see summarized data below), all of which were lower than the extractable limitation concentrations

Leached Compound	Concentration (µg/g product)		L_{max} of MHEL Model	Ratio of X & L_{max}	
	Average, X	Range			
	Mean ± SD, s	Min Max	µg/g	X/L_{max} %	L_{max}/X
[redacted]					

The following specifications were proposed by the sponsor to control the leachable compounds in commercial E004 drug product:

[redacted]

[2] The sponsor referred to a document by [redacted] level; see: \\cdsesub1\evsprod\nda205920\0026\m3\32-body-data\32p-drug-prod\epinephrine-hfa-inhalation-aerosol\32p7-cont-closure-sys\mdi-valves.pdf

These specifications would produce daily doses of (b) (4) that are considered acceptable based on assessments of these leachables in previously approved products.

The limit of (b) (4) µg/g product for (b) (4) would produce a daily dose to these oligomers of approximately (b) (4) µg. This is based on 8 inhalations per day and (b) (4) mg of product/inhalation. (b) (4) but still acceptable in light of the fact that (b) (4) do not possess structural alerts for irritation or genetic toxicity and the finding that the actual levels detected in the 3 batches tested to date are well below the maximum recommended levels for this leachable.

Integrated Summary and Safety Evaluation

Epinephrine HFA MDI is being considered as a replacement for the Primatene Mist which was removed from the market to eliminate CFC-containing products. No new nonclinical studies have been performed or are needed for the justification of the safety profile of epinephrine for this NDA. Epinephrine was previously approved as the active ingredient in Primatene Mist and no outstanding nonclinical concerns exist regarding the drug substance. Epinephrine is a Pregnancy Category C drug based on nonclinical studies and should be used in pregnancy only if the benefit justifies any potential fetal risk.

The safety of HFA 134a has been addressed in previous pharmacology/toxicology reviews (see appendix 1). Briefly, HFA in MDIs was not found to be carcinogenic, mutagenic or biologically reactive and does not seem to accumulate in tissues, usually being exhaled intact almost immediately after inhalation. Genetic toxicology, reproductive, acute, subchronic and chronic inhalation, toxicokinetic, cardiac sensitization, and carcinogenicity studies were all conducted to support the safety of HFA 134a.

The inactive ingredients have been previously used in chronically inhaled products except for thymol, [redacted] The anesthesia indication is not considered a chronic indication. Exposure to thymol by other routes such orally through foods supports the systemic safety of thymol at the doses associated with this product. Acute inhalation safety of [redacted]% thymol also appears to be supported based on previous human use. The clinical studies conducted to support this NDA used the same formulation where patients had mean total exposure of 131 days (about 5 months). If clinical inhalation safety data are considered adequate then the use of [redacted]% thymol in the product may be acceptable from a safety perspective and no further nonclinical studies may be needed to support this concentration. However, nonclinical information is inadequate, on its own, to support the safety of chronically inhaled thymol because no repeated dose inhalation toxicity data are available. Nonclinical data would provide histopathology analysis which could be used to assess the long term effects of thymol on the lungs when used via the inhalation route of exposure.

The specifications for impurities and leachables appear acceptable from a pharm/tox perspective.

Appendix/Attachments

1. Pharmacology/Toxicology review for HFA-134a

2. **Safety review of thymol**[3]

(b) (4)

MSDS sheet information[4]

The material safety data sheet (MSDS) under conditions of occupational exposure to thymol indicates a number of safety issues when it is inhaled including irritation to the throat and lungs in some individuals. Persons with impaired respiratory function, airway diseases and conditions such as emphysema or chronic bronchitis, may incur further disability if excessive concentrations of particulate are inhaled.
Inhalation of aerosols (mists, fumes), generated by the material during the course of normal handling, may be damaging to the health of the individual.

TOXICITY AND IRRITATION (unless otherwise specified data extracted from RTECS - Register of Toxic Effects of Chemical Substances)

TOXICITY

Oral (rat) LD50: 980 mg/kg
Subcutaneous (Rat) LD_{50}: 1600 mg/kg
Oral (Mouse) LD_{50}: 640 mg/kg
Intraperitoneal (Mouse) LD_{50}: 110 mg/kg
Subcutaneous (Mouse) LD_{50}: 243 mg/kg
Intravenous (Mouse) LD_{50}: 100 mg/kg
Intravenous (Dog) LD_{50}: 150 mg/kg
Oral (Cat) LD_{50}: 250 mg/kg

[3] References used for the toxicity data for thymol: Health Canada report on thymol; Publication # 100360, published July 2010; EPA Registration Action Document (RED) on thymol
[4] http://datasheets.scbt.com/sc-215984.pdf

Oral (Rabbit) LD_{50}: 750 mg/kg Intravenous (Rabbit) LD_{50}: 60 mg/kg

Thymol can cause severe irritation to the eye and is corrosive to skin rabbit.

Health Canada toxicology summary for thymol:

Study Type[5]	Species	Result	Comment
Acute Toxicity of Thymol E_9509758			
Oral	Mice	LD_{50} = 640 mg/kg bw	Moderately acute toxicity
Dermal	Mice and Rats	LD_{50} ranges between 1049 mg/kg bw in mice and 2000 mg/kg bw in rats	Slightly acute toxicity
Inhalation	Based on known clinical use of thymol in humans.		Low toxicity
Skin irritation	Thymol is known for its corrosiveness based on published literatures.		Extremely irritating
Eye irritation			Extremely irritating
Skin sensitization	Based on published studies, thymol is a known sensitizer.		Potential skin sensitizer

General toxicity for thymol

In a 19-week study, groups of five male and five female weanlings Osborne- Mendel rats were fed 0 (control), 1000 or 10,000 ppm of food grade thymol in the diet. Body weights, food intake and general condition were recorded weekly. Hematological parameters and organ weights for liver, kidneys, spleen, heart, and testes were assessed at study termination. The tissues of all rats were examined macroscopically at death. There were no growth, hematological or macroscopic changes in the tissues noted in either dose group, compared with the control group. In addition, microscopic

[5] This table is modified from Health Canada report on thymol

analysis of tissues was performed only for rats in the high-dose group and no changes were noted.

Prenatal/Developmental Toxicity

The prenatal developmental toxicity of thymol was investigated using developing chicken embryos. Thymol was injected into chicken embryos via the air cell and the yolk. Each injection group was treated at two stages of incubation: pre-incubation (0 h) and on the fourth day (96 h of incubation). At pre-incubation, thymol caused 0% to 36.13% and 1.73% to 15.65% of embryos to develop abnormally when treated via the air cell and the yolk sac, respectively. At 96 h of incubation, thymol caused 0% to 13.57% and 0.90% to 6.36% of embryos to develop abnormally when treated via the air cell and the yolk sac, respectively. The incidence of abnormal embryo development was statistically sig significant compared to controls for the air cell treatment, but not for the yolk treatment with thymol. The significance of these findings to humans is unknown given the differences in developmental physiology and anatomy between avian and mammalian species.

Genotoxicity

A number of in vivo and in vitro studies were available to assess the genotoxic potential of thymol. However, mixed findings have been reported. Thymol (99.73% pure) was tested for mutagenic potential in the Salmonella/microsome assay (standard plate incorporation test) using *Salmonella typhimurium* strains TA 98, TA 100, TA1535 and TA 1537. The tests were carried out in the presence and absence of metabolic activation (S-9 mix from Aroclor 1254-induced rat liver).The test concentrations ranged from 6 to 5000µg/plate. At higher concentrations, thymol showed varying degrees of bacterial toxicity, depending on the strain. Thymol was not observed to produce any genotoxic effects in this test system. Negative findings were also reported in similar studies.

Thymol (99.5% purity) was investigated for its genotoxic potential using V79 Chinese hamster lung fibroblast cells. The cells were treated with (b) (4) µM thymol for 30

minutes. The comet assay with formamido pyrimidine glycosylase protein was used. The results showed a lack of clastogenic activity for thymol at biologically relevant concentrations.

In addition, according to a recent in vivo genotoxicity study, groups of four Sprague-Dawley rats (two male and two female) were intraperitoneally treated with thymol (99.6% purity) at doses of 40, 60, 80 and 100 mg/kg body weight for 6, 12 and 24 h. Significant induction of structural and total chromosome abnormalities was observed in bone marrow cells of rats in all the concentrations and treatment times. Cytotoxicity from a decrease in the mitotic index was also observed at all test concentrations and treatment times. Although genotoxicity was observed in this study, these effects were noted at cytotoxic doses.

The genotoxic effects of thymol were also investigated using sister chromatid exchange, chromosome aberration, and micronucleus tests in human peripheral lymphocyte cells. The cells were treated with (b) (4) µg/mL concentrations of thymol (99.6% purity) for 24 h and 48 h treatment periods. Induction of sister chromatid exchange, structural chromosome aberration and frequency of micronucleus were observed in all treatment groups and times, as were cytotoxic effects measured by decreases in the replication, mitotic and nuclear division indices.

Further, groups of 15 A/He mice per sex per dose received intraperitoneal injections of thymol three times a week for eight weeks. The total thymol dose per mouse was 1.2 or 6.0 g/kg body weight. The results reported that thymol was negative for inducing primary lung tumors in mice. Overall, the weight of evidence suggests that thymol is not genotoxic or mutagenic at non-cytotoxic doses.

Chronic Toxicity/Carcinogenicity

No published data exist for the effects of chronic or carcinogenic effects for thymol.

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/s/

WAFA HARROUK
05/01/2014

PAUL C BROWN
05/02/2014
I concur with the conclusion and recommendation.

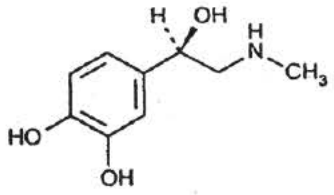
PHARMACOLOGY/TOXICOLOGY SAFETY REVIEW

IND number: 74,286
Review number: 1
Sequence number/date/type of submission: SN000, October 23, 2009, initial IND
Information to applicant: Yes () No (x)
Applicant and/or agent: Armstrong Pharmaceuticals, Inc.
Manufacturer for drug substance: (b) (4)

Reviewer name: Cindy Li, Ph.D.
Division name: Division of Non-Prescription Clinical Evaluation
HFD #: 560
Review completion date: November 6, 2009

Drug:

Trade name: Epinephrine Inhalation Aerosol USP
Generic name: Epinephrine Inhalation Aerosol USP
Synonyms: Adrenaline
Chemistry name: (-)-3,4-Dihydroxy-α-[(methylamino)methyl] benzyl alcohol
CAS registry number: 51-43-4
Molecular formula: C9H13NO3
Molecular weight: 183.20
Structure:



Drug class:

Relevant INDs/NDAs/DMFs:
NDA 16-126 Wyeth, Primatene® Mist
ANDA 87-907 Armstrong Pharmaceuticals, Inc., Epinephrine Inhalation Aerosol
[DMF (b) (4)
[DMF (b) (4)
[DMF
[DMF
[TBD*] (b) (4)

(b) (4)

.

Relevant previously marketed products: Primatene® Mist under Wyeth's NDA 16-126, approved on November 08, 1967 and Armstrong's Epinephrine Inhalation Aerosol USP, ANDA 87-907, approved on May 23, 1984 for treating mild asthma symptoms.

Intended clinical population: Temporary relief of occasional symptoms of mild asthma including wheezing, tightness of chest, and shortness of breath

Route of administration: Inhalation

Clinical formulation:
The drug formulation is presented in the following table provided from the applicant's submission:

Table 3-7 Unit Dose Compositions of the proposed IND product, E004, for the Proposed E004 Clinical Study A (a Phase I/II Study)

	Proposed Formulations for E004 IND			
Strength	90 mcg/spray	125 mcg/spray	160 mcg/spray	220 mcg/spray
Unit Composition (% w/w)				
API: Epinephrine USP (b) (4)	(b) (4)			(b) (4)
Inactive Ingredients: (b) (4) Polysorbate 80, NF				
Dehydrated alcohol USP	1.0000	1.0000	1.0000	1.0000
Thymol NF				(b) (4)
(Propellant) HFA-134a				
Filling amount, g/unit				

Background:

Epinephrine chlorofluorocarbon metered-dose inhaler has been available over-the-counter (OTC) since the 1960s and used by asthmatic patients for self-therapy. The dosage for adults and children 4 years of age and older is 1 to 2 inhalations of a metered-dose equivalent to (b) (4) mcg epinephrine per inhalation not to be taken more often than every 3 hours.

The propellants used in epinephrine MDIs and most other aerosolized asthma medications have traditionally been chlorofluorocarbons (CFCs). Because CFCs have been implicated in the accelerated depletion of ozone in the environment, FDA published a final rule on November 19, 2008 to remove the "essential-use" designation for epinephrine administered in oral pressurized metered-dose inhaler using CFCs as a propellant. The rule will effectively bar the production, marketing and sale of epinephrine CFC inhalers after December 31, 2011.

Amphastar Pharmaceuticals, Inc, on behalf of its subsidiary, Armstrong Pharmaceuticals, Inc., proposes the product, Epinephrine Inhalation Aerosol USP, propelled by a hydrofluoroalkane (HFA) in replacement of the currently approved epinephrine product

propelled by CFC. This product is for temporary relief of occasional symptoms of mild asthma such as wheezing, tightness of chest, and shortness of breath.

The present IND is opened with a clinical protocol entitled: "A randomized, double-blinded or evaluator blinded, placebo and active controlled, six-arm, crossover, single-dose, dose-ranging study, for initial evaluation of safety and efficacy in asthma patients". The objectives of the study are to evaluate the efficacy and safety of HFA-134a E004 formulation, in comparison to the placebo (placebo-HFA) and an active control (epinephrine CFC-MDI), and to identify the optimum E004 dose strengths for the ensuing pivotal clinical trials. The trial will be conducted in approximately 24 adult subjects who have intermittent, or mild-to-moderate persistent asthma for at least 6 months.

Previous clinical experience: There is no reported clinical experience with the combination of Epinephrine and HFA134a. However, epinephrine has been previously marketed and used by humans under the monograph and HFA134a has been used in several FDA-approved drug products.

Studies reviewed within this submission: No new nonclinical studies were submitted for review at this time. This application is in preparation to submission of a 505(b)(2) NDA which will relying on the Agency's previous findings of efficacy and safety of inhaled epinephrine for treating mild asthma symptoms. This IND references both the reference listed product (RLD), Primatene® Mist under Wyeth's NDA 16-126, approved on November 08, 1967 and Armstrong's Epinephrine Inhalation Aerosol USP, ANDA 87-907, approved on May 23, 1984. Both NDA 16-126 and ANDA 87-907 are epinephrine CFC-MDI products. Subsequent to Armstrong's purchase of the Primatene® Mist trademark, Wyeth withdrew NDA 16-126 and discontinued distribution of this product.

Epinephrine is listed under the monograph 21CFR341.16. The propellant HFA-134a has been used in a list of FDA-approved products such as PROVENTIL. HFA-134a is devoid of pharmacological activity except at very high doses in animals, primarily producing ataxia, tremors, dyspnea, or salivation. The International Pharmaceutical Aerosol Consortium for Toxicity Testing (IPACT) and/or the Program for Alternative Fluorocarbon Toxicology Testing conducted the safety studies. These previous safety studies showed that the HFAs were not biologically reactive, not carcinogenic, not mutagenic, and there was no target organ or tissue accumulation.

All excipients used in this product (in the table above under *clinical formulation*) appear to pose no safety concern for the proposed single dose clinical trial from the nonclinical perspective.

Nonclinical safety issues relevant to clinical use: None at this time.

Overall conclusions: The proposed single dose clinical study appears reasonably safe to proceed from the Pharmacology/Toxicology perspective based on the previous human

use for both epinephrine and HFA134a and the other supporting nonclinical information summarized by the sponsor.
Comments to applicant: None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-74286	ORIG-1	AMPHASTAR PHARMACEUTICAL INC	EPINEPHRINE HFA INHALATION AEROSOL

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

/s/

XINGUANG LI
11/25/2009

PAUL C BROWN
11/25/2009