CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210598Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210598
Review #1

Drug Name/Dosage Form	Yupelri (revefenacin inhalation solution)
Strength	(b) (4) 175 mcg
Route of Administration	oral inhalation
Rx/OTC Dispensed	Rx
Applicant	Theravance Biopharma US, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*13-NOV-2017*	*All*
Amendment	*29-JAN-2018*	*drug product (labeling)*
Amendment	*09-FEB-2018*	*drug product, process, microbiology*
Amendment	*22-FEB-2018*	*drug product*
Amendment	*13-MAR-2018*	*microbiology*
Amendment	*22-MAR-2018*	*drug product*
Amendment	*06-APR-2018*	*drug substance*
Amendment	*30-APR-2018*	*process*
Amendment	*30-APR-2018*	*OTR (methods verification in progress)*
General Correspondence	*27-JUN-2018*	*drug product (labels)*
Amendment	*11-JUL-2018*	*drug product*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Paresma Patel	Donna Christner
Drug Product	Valerie Amspacher	Craig M. Bertha
Process	Jonathan Swoboda	Joanne Wang
Microbiology	Yan Sheng	Erika Pfeiler
Facility	Jonathan Swoboda	Ying Zhang
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Bamidele (Florence) Aisida	

Application Technical Lead	Craig Bertha	
Laboratory (OTR)	N/A	
ORA Lead	Rachel Cook	
Environmental	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

. DMFs:

	Type			Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Not reviewed – sufficient information in application		
	Type III			**Adequate** – no revision since review	31-MAR-2011	
	Type III			**Adequate** – no revision since review	15-SEP-2014	Reviewed in (b) (4)

B. Other Do *applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	119840	IND for inhalation solution supporting this NDA

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

N/A

II. Summary of Quality Assessments

A. Product Overview

Revefenacin is a new molecular entity intended to treat COPD patients. The drug product is an inhalation solution to be delivered via general-use nebulizers. The drug is an anticholinergic and several other anticholinergic drug products for COPD are already approved (inhalation powders, inhalation sprays), but none as inhalation solutions. The sterile aqueous-based formulation has a target pH of 5.0 and includes common excipients for (b) (4) used in other inhalation solution products (as per Inactive Ingredient Guide). The solution is filled into LDPE vials using (b) (4) using a (b) (4) already used for another approved inhalation solution drug product. The filled vials are overwrapped with foil laminate, which is typical, since LDPE vials are semi-permeable.

Proposed Indication(s) including Intended Patient Population	Revefenacin inhalation solution is an anticholinergic indicated for the (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD), (b) (4) (b) (4)
Duration of Treatment	Chronic
Maximum Daily Dose	175 mcg revefenacin by oral inhalation daily (*q.d.*)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Revefenacin is a small molecule long-acting muscarinic receptor antagonist being developed as an inhalation solution for administration via a general-use nebulizer. Revefenacin, free base, is an anhydrous, crystalline and thermodynamically stable form that is highly soluble in aqueous buffered solution at pH 5. The drug substance is a white to off-white, achiral, crystalline powder. The selected anhydrous crystal form of Revefenacin (Form 1) is the most thermodynamically stable form. A second (b) (4) form (Form 2) (b) (4) (b) (4) forms are also known. However, the drug substance has been consistently produced as the thermodynamically favorable

(b) (4)

to minimize any impact on the purity of the final drug substance. Clinical and registration drug substance batch data are provided and are within specification acceptance criteria. The proposed retest period of revefenacin drug substance o

(b) (4)

The drug product is formulated with compendial grade excipient

(b) (4)

evaluation). The drug product formulation is an isotonic, sterile aqueous solution containing sodium chloride, citric acid, and sodium citrate, at pH 5.0. Standar (b) (4) technology is used to package the solution formulation and the control strategy for leachables from the container (low density polyethylene or LDPE) and foil laminate overwrap was found to be adequate, considering the extractables and leachables data provided. The drug product specifications are in line with the recommendations in Agency guidance,[1] are reflective of the data provided, and the associated methods appear to be validated. Based on ICH guideline Q1E, the stability data for the drug product support a **24 month shelf-life**. There were no significant changes on stability when drug product was stored at 25°C/60%RH for 12 months and 40°C/75%RH for 6 months. The product will be labeled to be stored at USP room temperature.

For the manufacturing of the formulation, ther

(b) (4)

during routine production. The drug product is a sterile solution provided in single-dose LDPE vials that are sealed in laminate foil pouches and inserted in a cardboard box as secondary packaging. The unit operations involved in the production of the subject drug product includ

(b) (4)

place during manufacturing to minimize high risk unit operations. Manufacturing of the pivotal clinical and registration batches was as proposed for the routine commercial production.

Inhalation solutions are required to be sterile, thus it is important that the applicant performs 100% leak testing on filled vials, and the associated validation of the test was found to be acceptable. Environmental monitoring an (b) (4) bioburden testing being performed were found to be acceptable as well. Th (b) (4) validation study performed and media fills were acceptable and the proposed holding periods are validated. Finally, the sterility testing procedure is acceptable, as

[1] *Guidance for Industry; Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation* (July 2002).

are the proposed storage condition and shelf life for the drug product, from a microbiology perspective.

Following the assessment of the application and inspectional documents, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 210598 are found to be acceptable.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

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MICROBIOLOGY

IQA Review Guide Reference

Product Background

NDA: 210598

Drug Product Name / Strength: Revefenacin. [redacted] 175 mcg/3mL. Single dose, inhalation solution.

Route of Administration: Inhalation

Applicant Name: Theravance Biopharma Ireland LTD

Manufacturing Site: [redacted]

Method of Sterilization: [redacted]

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): Choose an item.

Review Summary:

List Submissions Being Reviewed: 11/13/2017; 02/09/2018; 3/13/2018

Highlight Key Outstanding Issues from Last Cycle: N/A.

Remarks: This is an eCTD submission.

Concise Description Outstanding Issues Remaining: N/A.

Supporting Documents:
The environmental monitoring of the same facility is approved in [redacted] on [redacted]

Leak testing validation study using [redacted] has been approved in [redacted]

S Drug Substance

No review was conducted on the drug substance as the drug product is [redacted] as reviewed below.

P.1 Description of the Composition of the Drug Product

- **Description of drug product** –Revefenacin is 3mL sterile inhalation solution product in a low-density polyethylene (LDPE) unit-dose vial. It is a single dose product [redacted] 175mcg/3mL.
  The product is used with a standard jet nebulizer containing [redacted] connected to an air compressor.

- **Drug product compo**

Component	[redacted]	W
Revefenacin [redacted]	[redacted]	[redacted]
Sodium chloride, USP	[redacted]	[redacted]
Citric acid [redacted]	[redacted]	[redacted]
Sodium citrate [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
WFI	[redacted]	[redacted]

- **Description of conta yste**
  [redacted] revefenacin.

	Components	Supplier
Primary packaging	LDPE vial [redacted]	[redacted]
Secondary packaging	Aluminum foil laminate	
Tertiary packaging	Paperboard shelf carton (contains 30 pouched vials)	N/P

Reviewer's Assessment: ***Adequate***

The product description is acceptable.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity (3.2.P.7, p9)

[redacted]

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(b) (4)

[redacted]

P. 8.1 Stability Summary and Conclusion

(b) (4) 175mcg/3mL (b) (4) stored at room temperature (20-25°C), with a shelf life of 24 months (3.2.P.8.1, p7).

(b) (4) [redacted]

This is a single use product, and it should be opened immediately before use. Any residual content should be discarded after use (1.14.1.3, p2).

Reviewer's Assessment: ***Adequate***

The proposed storage condition and shelf life are acceptable.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to continue the stability for registration stability batches of 175mcg/3mL revefenacin (6GD4-1, 6GD5-5, 6GD6-5) (b) (4) (b) (4)

One 175mcg/3mL batch (b) (4) will be placed on the stability program annually after commercial production. Routine stability program: batch samples are placed at long term condition at 25±2°C/60±5% RH, and sterility test is performed at 0, 12, 24, 36, and 48 months (3.2.P.8.2, p1).

Reviewer's Assessment: ***Adequate***

The post-approval stability protocol and commitment are acceptable.

P.8.3 Stability Data

Sterility test for 175mcg/3mL (b) (4) (3.2.P.8.1, p4):

Storage condition	Parameters	Sterility test frequency
Long term	25±2°C/60±5% RH	0, 12, 18, 24, 36, 48 months
Intermediate	30±2°C/65±5% RH	0, 6, 12 months
Accelerated	40±2°C/75±5% RH	0, 6 months

Stability samples stored at intermediate condition are optional and are only tested in case of significant changes at the accelerated condition (3.2.P.8.1, p2).

Stability data for three 175mcg/3mL registration batches (6GD4-1, 6GD5-5, 6GD6-5) (b) (4) are available up to 12 month at long term condition and up to 6 months at accelerated condition. All samples remained sterile after 12 months storage at long term condition and 6 month storage at accelerated condition (3.2.P.8.3).

No in-use sterility data is needed, because this is a single-use product and the drug is used immediately after opening.

Reviewer's Assessment: ***Adequate***

The provided stability data is supportive of a 24-month shelf life at room temperature.

A Appendices-N/A

R Regional Information

Executed Batch Reords

Executed lot #(s): 6GD4 (175mcg/3mL) (b) (4)

The batch records confirm that validated (b) (4) manufacturing processes were used for the manufacture of the exhibit batch.

(b) (4)

(b) (4)

Reviewer's Assessment: ***Adequate***

The provided batch record is acceptable.

Comparability Protocols-N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

The 175mcg/3mL vial is stored at room temperature (20-25°C), protected from sunlight

(b) (4)

Primary Microbiology Reviewer Name and Date:

Yan Zheng, Ph.D. 3/14/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Erika Pfeiler, Ph.D. QAL

Yan Zheng

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Erika Pfeiler

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Attachment - OPQ Risk Assessment (RA) - NDA 210598

DP attribute/ CQA	Factors that may impact the CQA	O[1]	S[1, 2]	D[1]	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Comments and/or Lifecycle considerations
Revefenacin (API) identity, assay, impurities	• incorrect API • incorrect amount of API formulated (incorrect concentration) • high impurity levels (low assay) of input API • high level of degradation of API as formulated • non-uniform fill volume or vial leak • leak in protective packaging leading to evaporation	3	3	2	18	(b) (4)		
pH	• changes in levels of acidic or basic impurities in formulation components (API, excipients) • incorrect amounts of excipients	2	3	1	6			

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability

[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of "3" will be used throughout)

Attachment - OPQ Risk Assessment (RA) - NDA 210598

Sterility[3]								
(b) (4)	• incorrect amount of sodium chloride added • leachables from LDPE (b) (4) of solution	2	3	1	6	(b) (4)		
Particulate matter	• particulate matter introduced during (b) (4)	3	3	2	18			
Leachables	• (b) (4) •	2	3	5 (2)	30		12	(b) (4)

[3] Evaluation to be done by the microbiology team

Attachment - OPQ Risk Assessment (RA) - NDA 210598

								(b) (4)
Uniformity of Dosage Units/net content	• non-uniform fill volume • vial leakage	3	3	2	18	• (b) (4) • •		

Craig Bertha

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