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RESEARCH**

APPLICATION NUMBER:

208294Orig1s000

CHEMISTRY REVIEW(S)

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NDA/BLA

NDA 208294

NDA-208294-ORIG-1

Project Owner

Brandi Wheeler

Status

• Current

Condition

In Trouble

Planned Completion

Apr 23, 2016

Percent Complete

72.6%

Project Actions

Project Summary

Project Details

Application History

Inspection View

Tasks

Updates

More

As of Apr 25, 2016 11:26 am GMT

Inspection View

New Task

Export

Details

Summary

Task Number	Task Name	Comments	Assignments	Pln Comp	Act Comp	Task Status	Actions	Additional Information
Parents Manufacturing Facility Inspection (2)								
(b) (4)								

Recommendation: Approval

NDA 208294

Review 1

Review Date

Drug Name/Dosage Form	Bevespi MDI (glycopyrrolate and formoterol fumarate) Inhalation Aerosol
Strength	9/4.8 mcg
Route of Administration	Oral Inhalation
Rx/OTC Dispensed	R _x
Applicant	Pearl Therapeutics, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	25-Jun-2015
General Correspondence (GC); IR response	30-Jul-2015
GC; IR response	26-Aug-2015
Amendment; filing letter response	17-Sep-2015
Amendment; IR response	16-Oct-2015
Amendment; IR response	20-Nov-2015
Amendment; IR response	08-Dec-2015
Amendment; IR response	21-Dec-2015
Amendment; IR response	12-Feb-2016
Amendment; IR response	14-Mar-2016

Quality Review Team

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Table of Contents

Table of Contents	2
Quality Review Data Sheet	3
Executive Summary	5
Primary Quality Review.....	10
ASSESSMENT OF THE DRUG SUBSTANCE	10
2.3.S DRUG SUBSTANCE	10
ASSESSMENT OF THE DRUG PRODUCT	26
2.3.P DRUG PRODUCT	26
R.2 Comparability Protocols.....	184
ASSESSMENT OF THE PROCESS.....	188
2.3.P DRUG PRODUCT	188
R.2 Comparability Protocols.....	253
ASSESSMENT OF THE FACILITIES	256
2.3.S DRUG SUBSTANCE	256
2.3.P DRUG PRODUCT	262
ASSESSMENT OF THE BIOPHARMACUETICS	267
ASSESSMENT OF MICROBIOLOGY	287
2.3.P.7 Container/Closure System	294
A APPENDICES	294
ASSESSMENT OF ENVIRONMENTAL ANALYSIS	296
I. Review of Common Technical Document-Quality (Ctd-Q) Module 1	297
Labeling & Package Insert.....	297
II. List of Deficiencies To Be Communicated.....	304
III. Attachments	304

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		
	V			3	Adequate	02-Dec-2011	See pharm/tox review
	III			3	Adequate	24-Apr-2016	
	IV			3	Adequate	17-Feb-2012	
	II			1	Adequate	06-Nov-2015	
	II			1	Adequate	06-Nov-2015	
	III			3	Adequate	19-Apr-2012	No significant changes since last review
	III			1	Adequate	30-Mar-2016	IR letter
	III			3	Adequate	19-Apr-2012	No significant changes since last review
	III			1	Adequate	07-Apr-2016	
	III			1	Adequate	06-Nov-2015	
	III			4	N/A		
	IV			1	Adequate	06-Jan-2016	
	III			1	Adequate	06-Jan-2016	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

³ Include reference to location in most recent CMC review

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21929	Symbicort® (budesonide/formoterol fumarate) Inhalation Aerosol
IND	107739	Glycopyrrolate/formoterol fumarate inhalation aerosol for COPD
(b) (4)		

2. CONSULTS:



QUALITY ASSESSMENT



DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH DMQ/OC				
Clinical				
Other				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

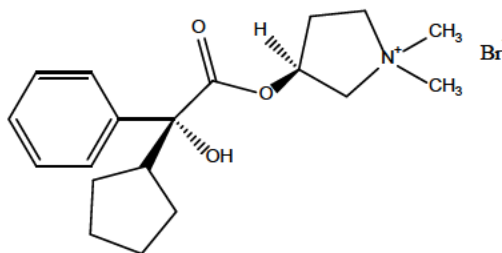
For the drug substances and the porous particles of the formulations, see the respective drug master file reviews. These drug product components were found to be adequate to support this application.

Pearl's combination drug/combination product (with glycopyrrolate/formoterol fumarate) is an inhalation aerosol with a suspension formulation of glycopyrrolate (antimuscarinic) and formoterol fumarate or FF (beta-agonist) in HFA-134a. (b) (4)

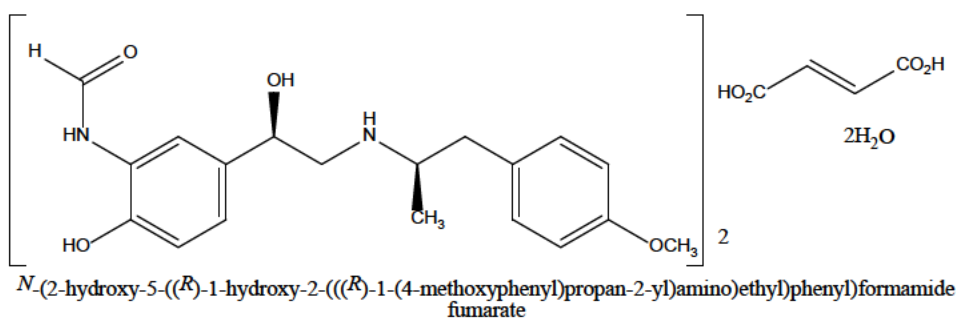
The drug product formulation is contained in a (b) (4) aluminum canister fitted with a crimped-on metering valve, plastic actuator/dust cap and a top of canister mounted dose indicator. The drug product also includes protective packaging in the form of a foil laminate with enclosed desiccant. The proposed proprietary name of the drug product is BEVESPI AEROSPHERE and the proposed indication is "for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)." The drug delivers 9.0 mcg of glycopyrrolate and 4.8 mcg of formoterol fumarate from the mouthpiece/actuation. The dosage is 2 inhalations twice daily (BID), or 36.0 mcg of glycopyrrolate and 19.2 mcg of formoterol fumarate per day. The applicant proposes a 24 month shelf life for the drug product and a 3 month in-use period (after removal of protective packaging). It is important to note that when the drug product is outside of the protective packaging, it takes up moisture and at some point after 3 months, the moisture content reaches a point at which there is a negative impact on the delivered dose uniformity or DDU (increased variability).

A. Drug Substances [glycopyrrolate and formoterol fumarate] Quality Summary

1. Chemical Name or IUPAC Name/Structure:



Glycopyrrolate (Glycopyrronium Bromide) [(*S*)-3-((*R*)-2-cyclopentyl-2-hydroxy-2-phenylacetate)-1,1-dimethylpyrrolidin-1-ium bromide and enantiomer]



and enantiomer

2. Properties/CQAs Relevant to Drug Product Quality

For both drug substances, purity, particle size distribution (PSD), (b) (4) are quality attributes that can directly impact the drug product quality, however, for glycopyrrolate, the control (b) (4)

3. List of starting materials: For this and remaining items, see reviews of DMFs (b) (4)

4. Suppliers of starting materials (site)

5. Summary of Synthesis

6. Process

7. Container Closure

8. Retest Period & Storage Conditions

B. Drug Product [Established Name] Quality Summary

1. Strength

The strength of the inhalation aerosol drug product is 9 mcg glycopyrrolate and 4.8 mcg formoterol fumarate per actuation from the actuator mouthpiece.

2. Description/Commercial Image

The drug product, BEVESPI AEROSPHERE (glycopyrrolate and formoterol fumarate inhalation aerosol) is a pressurized metered-dose inhaler for delivery of a combination of micronized glycopyrrolate and micronized formoterol fumarate to patients by oral inhalation. It is formulated with hydrofluoroalkane (HFA-134a) propellant as a pressurized metered dose inhaler (MDI) containing 120 actuations/inhalations with a white plastic actuator body and mouthpiece with an orange dust cap. The MDI also incorporates a top-mounted dose indicator which indicates the number of remaining inhalations in decrements of 20, and advances every 10 inhalations.

After priming, each actuation of the inhaler meters 10.4 mcg of glycopyrrolate (equivalent to 8.3 mcg of glycopyrronium) and 5.5 mcg of formoterol fumarate from the valve. This results in the delivery of 9.0 mcg of glycopyrrolate (equivalent to 7.2 mcg of glycopyrronium) and 4.8 mcg of formoterol fumarate from the actuator mouthpiece under defined laboratory conditions. The actual amount of drug delivered to the lungs of patients depends on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system. The drug product formulation also contains porous particles that form a co-suspension with the micronized drug particles. The porous particles are comprised of the phospholipid (1,2- Distearoyl-*sn*-Glycero-3-Phosphocholine or DSPC) and calcium chloride.

3. Summary of Product Design (see section 2 above)
4. List of Excipients: (see section 2 above)
5. Process Selection (Unit Operations Summary)

(b) (4)



(b) (4)

6. Container Closure

Apart from the top-mounted dose indicator, the components of the drug product container closure system are quite typical (i.e., a canister, valve, actuator, foil laminate with desiccant).

7. Expiration Date & Storage Conditions:

24 month shelf-life with 3 month in-use period after overwrap opening; storage at controlled room temperature 20-25°C

8. List of co-packaged components: N/A, by Agency definition an inhalation aerosol drug product consists of the formulation, container, the valve, the actuator, and any associated accessories (i.e., the dose indicator) or protective packaging.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Bevespi Aerosphere™
Non Proprietary Name of the Drug Product	Inhalation aerosol
Non Proprietary Name of the Drug Substance	Glycopyrrolate and formoterol fumarate
Proposed Indication(s) including Intended Patient Population	Chronic obstructive pulmonary disease (adults)
Duration of Treatment	chronic
Maximum Daily Dose	2 inhalations BID
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification: Not provided by applicant

- Drug Substance:
- Drug Product:

2. Biowaivers/Biostudies N/A

- Biowaiver Requests
- PK studies
- IVIVC

E. Novel Approaches N/A

F. Any Special Product Quality Labeling Recommendations N/A from
quality perspective

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

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

history but however deferred to CDER. At the time the consult was received, the above inspection of (b) (4) had already occurred. As a result, CDER recommends a device inspection of this facility during the next drug surveillance inspection.

Quallyna Porte
Biologist, OPQ/OPF/DIA/BII
4/20/2016

Secondary Review Comments and Concurrence:

Derek S. Smith, Ph.D. 4/21/2016

ASSESSMENT OF THE BIOPHARMACUETICS

18. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

The proposed drug product, glycopyrronium and formoterol fumarate (GFF) inhalation Aerosol (referred to as Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (MDI), GFF MDI), is a combination of glycopyrronium (GP), an orally inhaled long acting muscarinic antagonist (LAMA), and formoterol fumarate (FF), an orally-inhaled selective long-acting B2 antagonist (LABA).

The earlier phase 1 studies used product formulated with (b) (4) formoterol fumarate co-suspended with micronized glycopyrronium bromide. In the subsequent clinical studies, product was formulated with (b) (4) porous particles co-suspended with micronized glycopyrronium bromide and micronized formoterol fumarate. This change did not affect the in vitro pharmaceutical performance of the product (b) (4).

Comparison of in vitro pharmaceutical performance was conducted on delivered dose uniformity and aerodynamic particle size distribution. No BA/BE comparison was conducted to bridge the change. Furthermore, Phase III clinical batches were used as the NDA stability batches, and they are the same as the commercial products in formulation.

Reviewer's Assessment:

The proposed drug product is an inhalation Aerosol product. There is no dissolution method and specification to review. The Biopharmaceutics review is focused on the bioavailability (BA) studies, which were conducted to compare the pharmacokinetics (PK) of GPP and FF components of the fixed dose combination product to respective mono-products, and to a loose combination of the mono-products.

1. BA Study PT0030901

Phase 1 BA studies PT0030901” A Randomized, Double-blind, Single Dose, Four-period, Four-treatment, Cross-over, Single-center Study Evaluating a Single Administration of Four Inhaled Treatments (PT001, PT003, PT005 Delivered Individually and PT001 and PT005 Delivered Together in Separate Inhalers) in Healthy Subjects”

Objectives: evaluate the safety and pharmacokinetics of a single dose of PT003 compared with single doses of PT001, PT005, and the loose combination of PT001+PT005 delivered from 2 separate inhalers in healthy subjects.

Number of subjects: 11 females and 5 males (mean age 27.4 years; range 19-47), received at least one study treatment.

Treatment arms:

1. Placebo MDI + GP MDI 72 µg (PT001)
2. Placebo MDI + FF MDI 9.6 µg (PT005)
3. Placebo MDI + GFF MDI 72/9.6 µg (PT003, or the fixed dose combination)
4. GP MDI 72 µg (PT001) + FF MDI 9.6 µg (PT005) (the loose combination)

This study used the initial formulations for GFF MDI and FF MDI, and that treatments were administered as four actuations (i.e., each subject received eight actuations at each treatment visit; four actuations for active treatment and/or four actuations for placebo). Plasma concentrations of glycopyrronium and formoterol were determined over 12 hours.

Results:**Table 1. Comparison of Relative BA Results of Glycopyrronium for GFF MDI versus GP MDI or Formoterol for GFF MDI versus FF MDI in Healthy Subjects and Subjects with COPD**

Study	Dose Levels	Ratio of Geometric LSM (%)	
		GFF MDI / GP MDI	
		AUC0-12	C _{max}
Healthy Subjects Study PT0030901	GFF MDI 72/9.6 µg* GP MDI 72 µg	51 (36, 72)	76 (51, 114)
Study	Dose Levels	Ratio of Geometric LSM (%) (90%	
		GFF MDI / FF MDI	
		AUC0-12	C _{max}
Healthy Subjects Study PT0030901	GFF MDI 72/9.6 µg FF MDI 9.6 µg	119 (113, 126)	115 (97, 137)

Table 2. Comparison of Relative BA Results of Glycopyrronium for GFF MDI (fixed combination) versus GP MDI Administered in Combination with FF MDI (loose combination) in Healthy Subjects

Study	Dose Levels	Ratio of Geometric LSM (%)	
		GFF MDI / GP MDI	
		AUC0-12	C _{max}
Healthy Subjects Study PT0030901	GFF MDI 72/9.6 µg vs. GP MDI 72 µg + FF MDI 9.6 µg	90 (49, 165)	69 (39, 121)

	GFF MDI 72/9.6 µg vs. FF MDI 9.6 µg + GP MDI 72 µg	70 (45, 109)	65 (40, 107)
	GFF MDI 72/9.6 µg vs. GP MDI 72 µg + FF MDI 9.6 µg (any order)	79 (57, 110)	67 (49, 92)

Table 3. Comparison of Relative BA Results of Formoterol for GFF MDI (fixed combination) versus FF MDI Administered in Combination with GP MDI (loose combination) in Healthy Subjects

Study	Dose Levels	Ratio of Geometric LSM (%)	
		GFF MDI / FF MDI	
		AUC0-12	C _{max}
Healthy Subjects Study PT0030901	GFF MDI 72/9.6 µg vs. GP MDI 72 µg + FF MDI 9.6 µg	97 (80, 116)	95 (66, 138)
	GFF MDI 72/9.6 µg vs. FF MDI 9.6 µg + GP MDI 72 µg	92 (78, 108)	86 (70, 106)
	GFF MDI 72/9.6 µg vs. GP MDI 72 µg + FF MDI 9.6 µg (any order)	94 (85, 105)	91 (75, 110)

- BA Study PT0030901 failed to meet the BE acceptance criteria.
- The PK of GP monotherapy was not bioequivalent to the PK of GP in the fixed dose combination treatment (GFF) or in the loose combination treatment.
- The formoterol AUC0-12 was comparable following dose of GFF MDI 72/9.6 relative to GP MDI 72 µg + FF MDI 9.6 µg in any order. The ratio of geometric LSM for AUC0-12 was 94%, with 90% CI of 85-105%, which meets the 80-125% bioequivalence acceptance criteria. The ratio of geometric LSM of C_{max} was 91%, with 90% CI of 75-110%, which fall outside of BE acceptance criteria.

In comparison to the monotherapy, the PK of FF increased following administration in combination with glycopyrronium. Ratios of geometric LSM for formoterol AUC₀₋₁₂ and C_{max} were 119% (90% CI: 113-126%) and 115% (90% CI: 97-137%), respectively, with 90% CI outside of BE acceptance criteria.

Bioanalytical method and validation report

Table 4. Validation report for formoterol and glycopyrrolate

	<u>Formoterol</u>	<u>Glycopyrrolate</u>
Linear Range	1.00 – 50.00 pg/mL	2.00 – 100.00 pg/mL
Lower Limit of Quantitation	1.00 pg/mL	2.00 pg/mL
Accuracy	102.0%	96.5%
Signal-to-Noise	32	199
Intra-Run Precision (CV)		
3.00 / 6.00 pg/mL	6.2%	1.6%
12.00 / 24.00 pg/mL	3.2%	2.1%
40.00 / 80.00 pg/mL	4.4%	2.1%
Intra-Run Accuracy		
3.00 / 6.00 pg/mL	108.0%	113.7%
12.00 / 24.00 pg/mL	91.3%	103.5%
40.00 / 80.00 pg/mL	100.3%	106.9%
Inter-Run Precision (CV)		
3.00 / 6.00 pg/mL	10.9%	8.8%
12.00 / 24.00 pg/mL	4.6%	6.7%
40.00 / 80.00 pg/mL	5.4%	5.6%
Inter-Run Accuracy		
3.00 / 6.00 pg/mL	100.7%	110.3%
12.00 / 24.00 pg/mL	91.5%	101.5%
40.00 / 80.00 pg/mL	95.1%	102.7%
Recovery (solvent)		
Analytes	43.4%	90.0%
Internal standards	36.2%	78.4%
Stabilities in Plasma		
Room Temperature	Up to 2 hours	Up to 6 hours
Refrigerated (4°C)	Up to 4 hours	Up to 6 hours
Frozen (-20°C)	At Least 12 days	At Least 12 days
Frozen (-80°C)	At Least 12 days	At Least 12 days
Freeze-Thaw Cycles at (4°C)	At Least 3 cycles	At Least 3 cycles
Processed Sample Stability (10°C)	At Least 24 hours	At Least 24 hours
Dilution Accuracy (HQC)		
x5	88.2%	91.0%
x10	85.9%	90.3%

For the room temperature stability, it is indicated for glycopyrrolate for up to 6 hrs, and is up to 2 hrs for formoterol. Glycopyrrolate is limited to 3 cycles in freeze-thaw stability, while formoterol is limited to 2 cycles in freeze-thaw stability. For glycopyrrolate and formoterol, the long-term (-80°C) freezer stability is 33 days.

A total of fifty-two (52) study samples from nine (9) subjects for formoterol and forty-five (45) samples from eight (8) subjects for glycopyrrolate were retested for the

purposes of incurred sample re-analysis. 97.8% (44/45) of the glycopyrrolate and 92.3% (48/52) of the formoterol ISR results met the acceptance criterion, which is 67% of the sample re-analysis results are within $\pm 20\%$ of their mean result.

The bioanalytical method and validation report are acceptable.

2. BA Study PT003010

A Phase I, Randomized, Double-Blind, Single-Dose, Four-Period, Four-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Two Doses of PT003 and Two Doses of PT001 in Japanese Healthy Subjects

Objectives: Evaluate the PK and the safety of two doses of GFF MDI and two doses of GP MDI in adult Japanese healthy subjects

Study Subjects: A total of 24 subjects (mean age 29.8 years, range 18-40) were randomized to one of the four treatment sequences

Treatment arms: Two dose levels of GFF MDI (28.8/9.6 μg and 14.4/9.6 μg) and GP MDI (28.8 μg and 14.4 μg) were administered by oral inhalation taken as 2 actuations

Results:

Table 5. Comparison of Relative BA Results of Glycopyrronium for GFF MDI versus GP MDI in Healthy Subjects and Subjects with COPD

Study	Dose Levels	Ratio of Geometric LSM (%)	
		GFF MDI / GP MDI	
		AUC0-12	C _{max}
Study PT003010	GFF MDI 28.8/9.6 μg vs. GP MDI 28.8 μg	(76.92, 107.62)	(79.79, 125.12)
	GFF MDI 14.4/9.6 μg vs. GP MDI 14.4 μg	88.01 (73.83, 104.92)	122.76 (97.03, 155.31)

- BA Study PT003010 failed to meet the BE acceptance criteria.

- The BE results suggest a decrease in bioavailability of glycopyrronium when administered as a combination therapy. Ratios of geometric LSM for AUC0-t and AUC0-12 were 83.76% (90% CI: 65.15-107.68%) and 90.98% (90% CI: 76.92-107.62%), respectively. There was no significant difference in glycopyrronium Cmax between GFF MDI 28.8/9.6 µg and GP MDI 28.8 µg, with a ratio of geometric LSM of 99.92% (90% CI: 79.79-125.12%).
- Glycopyrronium AUCs were slightly lower following the administration of GFF MDI 14.4/9.6 µg in comparison to GP MDI 14.4 µg with ratios of geometric LSM for AUC0-t and AUC0-12 of 89.48 (90% CI: 68.8-116.39%) and 88.01 (90% CI: 73.83-104.92%), respectively, with lower bound of 90% CI slightly outside of BE criteria. On the other hand, an increase in glycopyrronium Cmax was observed when administered as a combination therapy with formoterol, with a ratio of geometric LSM of 122.76% (90% CI: 97.03-155.31%).
- The PK of FF in the 28.8/9.6 µg fixed dose combination treatment was comparable to the PK of FF in the 14.4/9.6 µg fixed dose combination treatment. The ratios of geometric LSM of formoterol AUC0-12, AUC0-t and Cmax parameters for GFF MDI 28.8/9.6 µg vs. GFF MDI 14.4/9.6 µg were 101.15% (90% CI: 86.87-117.78%), 104.42% (90% CI: 86.90-125.48%) and 98.73% (78.26-124.54%), respectively. However, the applicant did not report the comparative BA of formoterol in the monotherapy and the fixed dose combination product.

Bioanalytical method validation:**Table 6A. Formoterol Validation Results**

Internal Standard:	Formoterol-d ₆
LLOQ and ULOQ:	1.00 pg/mL and 200 pg/mL
Calibration Standard Concentrations:	1.00, 2.00, 5.00, 10.0, 60.0, 120, 180 and 200 pg/mL
Inter-Assay Accuracy (%Bias):	-1.6% to 3.0%
Inter-Assay Precision (%CV):	1.7% to 12.0%
Regression and Weighting:	Linear 1/x
Quality Control Levels:	1.00, 3.00, 15.0, 80.0 and 160 pg/mL

LLOQ QC	
Intra-Assay Accuracy (%Bias):	-6.1% to -3.0%
Intra-Assay Precision (%CV):	1.5% to 9.1%
Inter-Assay Accuracy (%Bias):	-4.7%
Inter-Assay Precision (%CV):	0.0%
Intra-Assay results are reported as ranges from the A/P runs.	
Inter-Assay results are reported as the result from the ANOVA calculations.	
Low, Low-Medium, Medium and High QC	
Intra-Assay Accuracy (%Bias):	-4.7% to 1.3%
Intra-Assay Precision (%CV):	1.0% to 4.3%
Inter-Assay Accuracy (%Bias):	-2.3% to -0.1%
Inter-Assay Precision (%CV):	0.6% to 2.7%
Intra-Assay results are reported as ranges from the A/P runs.	
Inter-Assay results are reported as ranges from the ANOVA calculations.	
Ability to Dilute:	800 pg/mL (DF=10)
Dilution Linearity:	8,000 pg/mL (DF=100)
Carryover of Analyte:	Carryover greater than acceptable limits detected. See Analytical Notes Section for discussion.
Carryover of Internal Standard:	No carryover detected
Method Selectivity:	Evaluated using 6 Lots of blank matrix
Selectivity Blanks:	No interference greater than acceptable limits detected at the retention times of interest.
Matrix Effects	
LLOQ Reproducibility in Matrix:	Accuracy (%Bias): 14.0% Precision (%CV): 3.3%
Matrix Factor Test:	<u>Matrix Factor (Low)</u> Analyte = 0.864 Internal Standard = 0.861 <u>Matrix Factor (High)</u> Analyte = 0.869 Internal Standard = 0.868 A matrix factor greater than 1 indicates ionization enhancement. A matrix factor less than 1 indicates ionization suppression.
IS-Normalized Matrix Factor Test:	IS-Normalized MF (Low) = 1.00 IS-Normalized MF (High) = 1.00
Interference	
Analyte Only:	No significant interference found at the retention time of interest for Analyte Only samples.

Internal Standard Only:	No significant interference found at the retention time of interest for IS Only samples.
Additional Compounds:	Budesonide (500 pg/mL) Quantitation of formoterol is not impacted by the co-administered compounds when present at the concentrations described above.
IS Recovery:	79.4%
Analyte Recovery:	77.7% (Low) 78.0% (Medium) 77.3% (High)
Solution Stability	
IS Solution Stability	
Bench-Top:	6 Hours in IPA: water (50:50 v/v) stored in a glass container at room temperature and protected from light.
Analyte Solution Stability	
Bench-Top:	6 Hours in DMF stored in a polypropylene container at room temperature and protected from light.
Long-Term Stock:	90 Days in DMF at 5 °C. Originally reported in TSLR07-043 [11.1] Any additional stability conducted for this study will be added either as an addendum or appendix to that report.
Long-Term Working:	43 Days in DMF stored in a polypropylene container at 5 °C and protected from light. Any additional stability conducted for this study will be added either as an addendum or appendix to this report.
Stability in Matrix	
Freeze-Thaw:	4 Cycles; stored at -70 °C and thawed in an ice bath
Bench-Top:	6 Hours at room temperature and 5 °C
Intermediate-Term:	24 Days at -70 °C demonstrated by on-going analysis of QC samples against freshly prepared standards
Long-Term:	42 Days at -20 °C and 103 Days at -70 °C
Reinjection Reproducibility:	167 Hours at 5 °C
Extract Stability:	67 Hours at 5 °C
Whole Blood Stability:	2 Hours at room temperature and 5 °C
Hemolysis:	No significant impact in samples with up to 2.0% hemolysis
Hyperlipidemia:	No significant impact in samples with hyperlipidemia (Triglycerides >300 mg/dL; Total Cholesterol >250 mg/dL)
Batch Size Evaluation:	Sample analysis runs may include up to 192 samples (including Standards, QCs, Blanks, Unknowns, etc.)

Table 6B. Glycopyrrolate Validation Results

Internal Standard:	Glycopyrrolate-d ₃
LLOQ and ULOQ:	1.00 pg/mL and 200 pg/mL
Calibration Standard Concentrations:	1.00, 2.00, 5.00, 10.0, 60.0, 120, 180 and 200 pg/mL
Inter-Assay Accuracy (%Bias):	-2.6% to 2.0%
Inter-Assay Precision (%CV):	1.3% to 6.1%
Regression and Weighting:	Linear 1/x
Quality Control Levels:	1.00, 3.00, 15.0, 80.0 and 160 pg/mL
LLOQ QC	
Intra-Assay Accuracy (%Bias):	-5.6% to -3.0%
Intra-Assay Precision (%CV):	5.2% to 9.9%
Inter-Assay Accuracy (%Bias):	-4.3%
Inter-Assay Precision (%CV):	0.0%
Intra-Assay results are reported as ranges from the A/P runs.	
Inter-Assay results are reported as the result from the ANOVA calculations.	
Low, Low-Medium, Medium and High QC	
Intra-Assay Accuracy (%Bias):	-7.3% to 2.3%
Intra-Assay Precision (%CV):	1.4% to 5.0%
Inter-Assay Accuracy (%Bias):	-4.7% to 0.3%
Inter-Assay Precision (%CV):	0.0% to 2.0%
Intra-Assay results are reported as ranges from the A/P runs.	
Inter-Assay results are reported as ranges from the ANOVA calculations.	
Ability to Dilute:	800 pg/mL (DF=10)
Dilution Linearity:	8,000 pg/mL (DF=100)
Carryover of Analyte:	Carryover greater than acceptable limits detected. See Analytical Notes Section for discussion.

Carryover of Internal Standard:	No carryover detected
Method Selectivity:	Evaluated using 6 Lots of blank matrix
Selectivity Blanks:	No interference greater than acceptable limits detected at the retention times of interest.
Matrix Effects	
LLOQ Reproducibility in Matrix:	Accuracy (%Bias): -1.9% Precision (%CV): 3.7%
Matrix Factor Test:	<u>Matrix Factor (Low)</u> Analyte = 0.960 Internal Standard = 0.888 <u>Matrix Factor (High)</u> Analyte = 0.897 Internal Standard = 0.889 A matrix factor greater than 1 indicates ionization enhancement. A matrix factor less than 1 indicates ionization suppression.
IS-Normalized Matrix Factor Test:	IS-Normalized MF (Low) = 1.08 IS-Normalized MF (High) = 1.01
Interference	
Analyte Only:	No significant interference found at the retention time of interest for Analyte Only samples.
Internal Standard Only:	No significant interference found at the retention time of interest for IS Only samples.
Additional Compounds:	Budesonide (491 pg/mL) Quantitation of glycopyrrolate is not impacted by the co-administered compounds when present at the concentrations described above.
IS Recovery:	82.3%
Analyte Recovery:	83.7% (Low) 82.6% (Medium) 80.4% (High)
Solution Stability	
IS Solution Stability	
Bench-Top:	3 Hours in IPA: water (50:50 v/v) stored in a glass container at room temperature and protected from light.
Analyte Solution Stability	
Bench-Top:	6 Hours in DMF stored in a polypropylene container at room temperature and protected from light.

Long-Term Stock:	168 Days in DMF stored in a polypropylene container at 5 °C and protected from light. Originally reported in TSLR13-059 [11.2] Any additional stability conducted for this study will be added either as an addendum or appendix to that report.
Long-Term Working:	43 Days in DMF stored in a polypropylene container at 5 °C and protected from light. Any additional stability conducted for this study will be added either as an addendum or appendix to this report.
Stability in Matrix	
Freeze-Thaw:	4 Cycles; stored at -70 °C and thawed in an ice bath
Bench-Top:	6 Hours at room temperature and 5 °C
Intermediate-Term:	24 Days at -70 °C demonstrated by on-going analysis of QC samples against freshly prepared standards
Long-Term:	42 Days at -20 °C and 103 Days at -70 °C
Reinjection Reproducibility:	167 Hours at 5 °C
Extract Stability:	67 Hours at 5 °C
Whole Blood Stability:	2 Hours at room temperature and 5 °C
Hemolysis:	No significant impact in samples with up to 2.0% hemolysis
Hyperlipidemia:	No significant impact in samples with hyperlipidemia (Triglycerides >300 mg/dL; Total Cholesterol >250 mg/dL)
Batch Size Evaluation:	Sample analysis runs may include up to 192 samples (including Standards, QCs, Blanks, Unknowns, etc.)

As Table 6 shows, analyte carryover was observed in control blanks following a ULOQ standard (Standard 8) at a level >20% of the lowest acceptable LLOQ standard (Standard 1) for both formoterol and glycopyrrolate in (b) (4) 14-053 Add Run 11. The Applicant considers the carryover to be an isolated event, since there was an absence of carryover in other validation runs.

One analyte contamination was observed for glycopyrrolate in Run 2 at >20% of the lowest acceptable standard. The Applicant considers as the contamination an isolated event since no other occurrences were reported other than this run.

For the incurred sample reanalysis to be acceptable, a minimum of 67% of the repeat values (repeat value minus original value) for all analytes must be within $\pm 20\%$ of the average of the original and repeat values. For formoterol, 59 of 80 samples (>73%) met the acceptance criterion; while for glycopyrrolate, 109 of 122 samples (>89%) met the acceptance criterion.

Overall, the bioanalytical method and validation report are acceptable.

3. BA Study PT010001

A Phase I, Randomized, Double-Blind Within Device, Single-Dose, Four-Period, Six-Treatment, Cross-Over Study Evaluating the Safety and Pharmacokinetics of Three Doses of Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (BGF MDI), One Dose of Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI), and Two Doses of Symbicort® Inhalation Aerosol in Healthy Volunteers

Objectives:

1. Determine a dose of budesonide that when formulated with glycopyrronium and formoterol fumarate in BGF MDI provides comparable systemic exposure (PK) to budesonide following administration of Symbicort MDI 320/9 µg (two inhalations of 160/4.5 µg)
2. To assess if a drug-drug interaction (DDI) occurred when budesonide was formulated with glycopyrronium and formoterol fumarate in BGF MDI compared to glycopyrronium and formoterol fumarate only in GFF MDI. To evaluate the safety and tolerability of the treatments administered; i.e., BGF MDI, Symbicort MDI and GFF MDI.

Study subjects: 84 subjects

Treatment arms:

- Budesonide, glycopyrronium, and formoterol fumarate inhalation aerosol administered as BGF MDI (320/14.4/9.6 µg) ex-actuator
- Budesonide, glycopyrronium, and formoterol fumarate inhalation aerosol administered as BGF MDI (160/14.4/9.6 µg) ex-actuator
- Budesonide, glycopyrronium, and formoterol fumarate inhalation aerosol administered as BGF MDI (80/14.4/9.6 µg) ex-actuator
- Glycopyrronium and formoterol fumarate inhalation aerosol administered as GFF MDI (14.4/9.6 µg) ex-actuator
- Budesonide and formoterol fumarate inhalation aerosol administered as Symbicort MDI (320/9 µg) ex-actuator
- Budesonide and formoterol fumarate inhalation aerosol administered as Symbicort MDI (160/9 µg) ex-actuator

Results:**Table 7. Comparison of Budesonide Pharmacokinetic Parameters (Not Dose-normalized) for BGF MDI vs. Symbicort (Safety Population)**

Comparison/ PK Parameter	Geometric LSM		Geometric LSM Ratio (%)	Ratio of 90% CI [a]
	BGF MDI	Symbicort MDI		
BGF MDI 320/14.4/9.6 µg vs. Symbicort 320/9 µg				
N	79	77	-	-
AUC ₀₋₁₂ (h*pg/mL)	1612.21	1406.39	114.63	106.13, 123.82
AUC ₀₋₄ (h*pg/mL)	1611.68	1406.65	114.58	106.05, 123.79
C _{max} (pg/mL)	472.04	461.47	102.29	91.45, 114.42
BGF MDI 160/14.4/9.6 µg vs. Symbicort 160/9 µg [a]				
N	26	28	-	-
AUC ₀₋₁₂ (h*pg/mL)	858.61	850.55	100.95	86.34, 118.03
AUC ₀₋₄ (h*pg/mL)	858.19	850.31	100.93	86.30, 118.03
C _{max} (pg/mL)	233.94	268.36	87.18	70.37, 107.99

BGF=budesonide, glycopyrronium and formoterol fumarate; LSM=least square means; MDI=metered dose inhaler.
[a] Between-subject comparison.
Source: Table 2.7.1

Table 8. Comparison of Glycopyrronium Pharmacokinetic Parameters for BGF MDI vs. GFF MDI

Comparison/ PK Parameter	Geometric LSM		Geometric LSM Ratio (%)	90% CI
	BGF MDI	GFF MDI		
BGF MDI 320/14.4/9.6 µg vs. GFF MDI 14.4/9.6 µg				
N	79	77	-	-
AUC ₀₋₁₂ (h*pg/mL)	10.82	10.71	100.95	86.11, 118.35
AUC ₀₋₄ (h*pg/mL)	8.35	8.09	103.28	85.80, 124.31
C _{max} (pg/mL)	8.28	7.19	115.10	98.57, 134.39
BGF MDI 160/14.4/9.6 µg vs. GFF MDI 14.4/9.6 µg				
N	26	77	-	-
AUC ₀₋₁₂ (h*pg/mL)	11.46	10.71	107.00	84.54, 135.44
AUC ₀₋₄ (h*pg/mL)	9.02	8.09	111.44	84.62, 146.77
C _{max} (pg/mL)	8.93	7.19	124.14	97.66, 157.81
BGF MDI 80/14.4/9.6 µg vs. GFF MDI 14.4/9.6 µg				
N	27	77	-	-
AUC ₀₋₁₂ (h*pg/mL)	11.28	10.71	105.25	83.18, 133.17
AUC ₀₋₄ (h*pg/mL)	9.26	8.09	114.41	86.82, 150.78
C _{max} (pg/mL)	7.53	7.19	104.62	82.48, 132.71

PK=pharmacokinetic; BGF=budesonide, glycopyrronium and formoterol fumarate, GFF=glycopyrronium and formoterol fumarate; MDI=metered dose inhaler; LSM=least square means; CI=confidence interval
Source: Table 2.8.1

Table 9. Comparison of Formoterol Pharmacokinetic Parameters for BGF MDI vs. Symbicort MDI

Comparison/ PK Parameter	Geometric LSM		Geometric LSM Ratio (%)	90% CI
	BGF MDI	Symbicort MDI		
BGF MDI 320/14.4/9.6 µg vs. Symbicort MDI 320/9 µg				
N	79	77	-	-
AUC ₀₋₁₂ (h*pg/mL)	53.66	39.73	135.08	125.46, 145.43
AUC ₀₋₄ (h*pg/mL)	52.58	38.05	138.18	126.82, 150.56
C _{max} (pg/mL)	10.55	8.82	119.58	108.42, 131.90
BGF MDI 160/14.4/9.6 µg vs. Symbicort MDI 160/9 µg				
N	26	28	-	-
AUC ₀₋₁₂ (h*pg/mL)	52.14	40.91	127.45	110.57, 146.91
AUC ₀₋₄ (h*pg/mL)	51.65	39.70	130.10	110.12, 153.71
C _{max} (pg/mL)	10.21	8.57	119.17	98.97, 143.50
BGF MDI 160/14.4/9.6 µg vs. Symbicort 320/9 µg				
N	26	77	-	-
AUC ₀₋₁₂ (h*pg/mL)	52.14	39.73	131.24	117.48, 146.62
AUC ₀₋₄ (h*pg/mL)	51.65	38.05	135.75	119.05, 154.79
C _{max} (pg/mL)	10.21	8.82	115.72	100.20, 133.64
BGF MDI 320/14.4/9.6 µg vs. Symbicort MDI 160/9 µg				
N	79	28	-	-
AUC ₀₋₁₂ (h*pg/mL)	53.66	40.91	131.18	117.85, 146.03
AUC ₀₋₄ (h*pg/mL)	52.58	39.70	132.44	116.87, 150.08
C _{max} (pg/mL)	10.55	8.57	123.15	106.90, 141.88
BGF MDI 80/14.4/9.6 µg vs. Symbicort MDI 320/9 µg				
N	27	77	-	-
AUC ₀₋₁₂ (h*pg/mL)	51.70	39.73	130.13	116.66, 145.16
AUC ₀₋₄ (h*pg/mL)	50.09	38.05	131.65	115.62, 149.91
C _{max} (pg/mL)	10.14	8.82	114.98	100.01, 132.19
BGF MDI 80/14.4/9.6 µg vs. Symbicort 160/9 µg				
N	27	28	-	-
AUC ₀₋₁₂ (h*pg/mL)	51.70	40.91	126.37	109.77, 145.49
AUC ₀₋₄ (h*pg/mL)	50.09	39.70	126.18	106.94, 148.87
C _{max} (pg/mL)	10.14	8.57	118.41	98.65, 142.14

PK=pharmacokinetic; BGF=budesonide, glycopyrronium and formoterol fumarate; MDI=metered dose inhaler; LSM=least square means; CI=confidence interval
Source: Table 2.9.1

Table 10. Comparison of Formoterol Pharmacokinetic Parameters for BGF MDI vs. GFF MDI

Comparison/ PK Parameter	Geometric LSM		Geometric LSM Ratio (%)	90% CI
	BGF MDI	GFF MDI		
BGF MDI 320/14.4/9.6 µg vs. GFF MDI 14.4/9.6 µg				
N	79	77	-	-
AUC ₀₋₁₂ (h*pg/mL)	53.66	51.73	103.73	96.54, 111.47
AUC ₀₋₄ (h*pg/mL)	52.58	51.10	102.89	94.38, 112.17
C _{max} (pg/mL)	10.55	9.49	111.18	101.36, 121.95
BGF MDI 160/14.4/9.6 µg vs. GFF MDI 14.4/9.6 µg				
N	26	77	-	-
AUC ₀₋₁₂ (h*pg/mL)	52.14	51.73	100.78	90.13, 112.70
AUC ₀₋₄ (h*pg/mL)	51.65	51.10	101.08	88.71, 115.18
C _{max} (pg/mL)	10.21	9.49	107.58	92.87, 124.63
BGF MDI 80/14.4/9.6 µg vs. GFF MDI 14.4/9.6 µg				
N	27	77	-	-
AUC ₀₋₁₂ (h*pg/mL)	51.70	51.73	99.93	89.55, 111.52
AUC ₀₋₄ (h*pg/mL)	50.09	51.10	98.03	86.23, 111.44
C _{max} (pg/mL)	10.14	9.49	106.90	92.69, 123.29

PK=pharmacokinetic; BGF=budesonide, glycopyrronium and formoterol fumarate; GFF=glycopyrronium and formoterol fumarate; MDI=metered dose inhaler; LSM=least square means; CI=confidence interval
Source: Table 2.9.1

Based on the bioequivalence assessments, the budesonide component of BGF MDI 320/14.4/9.6 µg provided comparable systemic exposure to the budesonide component of Symbicort MDI 320/9 µg. However, the formoterol component in BGF MDI was not bioequivalent to that of Symbicort MDI.

The formoterol component was bioequivalent when BGF MDI 320/14.4/9.6 µg was compared to GFF MDI. In contrast, for the glycopyrronium component, the LSM ratio is within the bioequivalence criterion, but the upper bound of 90% CI was out of the range.

The PK of glycopyrronium and formoterol after single dose administration of GFF MDI are shown as follows:

Arithmetic Mean Pharmacokinetic Parameters (±SD)									
Glycopyrronium					Formoterol				
C _{max} (pg/mL)	T _{max} (h)	t _{1/2} (h)	AUC ₀₋₁₂ (pg.h/mL)	CL/F (L/h)	C _{max} (pg/mL)	T _{max} (h)	t _{1/2} (h)	AUC ₀₋₁₂ (pg.h/mL)	CL/F (L/h)
11.574	0.100	2.323	18.208	708.306	11.033	0.583	4.805	55.554	125.992

The PK parameters of glycopyrronium and formoterol after single dose of GFF MDI 14.4/9.6 µg were comparable to those observed in other studies.

Bioanalytical method and validation report:

Table 11 Bioanalytical methodology summary and performance for formoterol and glycopyrrolate

Assay Methodology Summary		
Method Validation Report	(b) (4) 3-059 [11.2]	
Matrix	Human Plasma	
Anticoagulant	K ₃ EDTA	
Type of Extraction	Solid-Phase	
Method of Detection	LC/MS/MS	
Sample Aliquot Volume	500 µL	
Quantitation	Peak Area Ratios	
Ionization Type	Electrospray, Positive	
MS Operation Mode	Selected Reaction Monitoring (SRM)	
Platform	API 6500	
Calibration Standard Distribution	Calibration standards were placed at the beginning and end of each bioanalytical run.	
Quality Control (QC) Distribution	QC samples were distributed throughout each bioanalytical run.	
Injection Sequence	The prepared samples, calibration standards and QCs were injected in a systematic order.	
Assay Carryover	Peaks greater than 20% of the lowest acceptable LLOQ analyte response that were attributable to carryover were not detected in control blank samples. It is (b) (4) policy to evaluate carryover in each acceptable analytical run. If peaks greater than 20% of the lowest acceptable LLOQ are detected in control blank samples, all study samples are reviewed on a sample by sample basis, and any potentially affected samples are repeated per SOP.	
Analyte	Formoterol	
Internal Standard	Formoterol-d ₆ (added to all samples except Blanks)	
Regression and Weighting	Linear 1/x	
LLOQ	1.00 pg/mL	
ULOQ	50.0 pg/mL	
Calibration Standard Concentrations	1.00, 2.00, 4.00, 8.00, 16.0, 32.0, 45.0 and 50.0 pg/mL	
Analytical QC Concentrations	3.00, 20.0 and 40.0 pg/mL	
Performance of Analytical QCs	Precision (%CV)	Accuracy (%Bias)
	3.8% to 9.1%	-0.5% to 5.0%
Run Performance (see Table 1)	No. of Accepted Runs	No. of Rejected Runs
	29	1
Analyte	Glycopyrrolate	
Internal Standard	Glycopyrrolate iodide-d ₃ (added to all samples except Blanks)	
Regression and Weighting	Linear 1/x	
LLOQ	2.00 pg/mL	
ULOQ	100 pg/mL	
Calibration Standard Concentrations	2.00, 4.00, 8.00, 16.0, 32.0, 64.0, 90.0 and 100 pg/mL	
Analytical QC Concentrations	6.00, 40.0 and 80.0 pg/mL	

Performance of Analytical QCs	Precision (%CV)	Accuracy (%Bias)
	3.8% to 6.8%	2.8% to 8.3%
Run Performance (see Table 1)	No. of Accepted Runs	No. of Rejected Runs
	29	0

Sample Storage Stability	
First Sample Collected to Last Sample Extracted (Theoretical Maximum) for Formoterol	108 days
First Sample Collected to Last Sample Extracted (Theoretical Maximum) for Glycopyrrolate	60 days
Demonstrated Storage Stability	280 days at -80 °C
Stability Data Reference	STAB-RPT-086 [11.5]
Samples Collected and Analyzed within Stability Limits	Yes

Incurred Sample Reanalysis (ISR)	
Incurred sample reanalysis samples were assayed in singlet in three analytical runs for formoterol and two analytical runs for glycopyrrolate.	
Samples Meeting Acceptance Criteria for Formoterol	310 out of 352 samples (88.1%)
Samples Meeting Acceptance Criteria for Glycopyrrolate	254 out of 276 samples (92.0%)
Incurred Sample Reanalysis was Acceptable for Formoterol	Yes
Incurred Sample Reanalysis was Acceptable for Glycopyrrolate	Yes

Table 12. Assay methodology and performance for budesonide

Method Validation Report	(b) (4) 13-225 [11.3]
Matrix	Human Plasma
Anticoagulant	K ₃ EDTA
Type of Extraction	Solid-Phase
Method of Detection	LC/MS/MS
Sample Aliquot Volume	500 µL
Quantitation	Peak Area Ratios
Ionization Type	Electrospray, Positive
MS Operation Mode	Selected Reaction Monitoring (SRM)
Platform	API 6500
Calibration Standard Distribution	Calibration standards were placed at the beginning and end of each bioanalytical run.
Quality Control (QC) Distribution	QC samples were distributed throughout each bioanalytical run.
Injection Sequence	The prepared samples, calibration standards and QCs were injected in a systematic order.

Assay Carryover	Peaks greater than 20% of the lowest acceptable LLOQ analyte response that were attributable to carryover were not detected in control blank samples. It is (b) (4) policy to evaluate carryover in each acceptable analytical run. If peaks greater than 20% of the lowest acceptable LLOQ are detected in control blank samples, all study samples are reviewed on a sample by sample basis, and any potentially affected samples are repeated per SOP.	
Analyte	Budesonide	
Internal Standard	Budesonide-d ₈ (added to all samples except Blanks)	
Regression and Weighting	Linear 1/x ²	
LLOQ	3.00 pg/mL	
ULOQ	500 pg/mL	
Calibration Standard Concentrations	3.00, 6.00, 12.5, 50.0, 100, 250, 450 and 500 pg/mL	
Analytical QC Concentrations	9.00, 40.0, 200 and 400 pg/mL	
Dilution QC Concentration	4,000 pg/mL	
Dilution Factor	DF=10	
Assay Methodology Summary		
Performance of Analytical QCs	Precision (%CV)	Accuracy (%Bias)
	3.9% to 11.2%	-0.8% to 0.3%
Run Performance (see Table 2)	No. of Acceptable Runs	No. of Rejected Runs
	31	2
Calibration Standards		
Date(s) of Preparation	03-Dec-2013 and 13-Jan-2014	
Matrix	Human Plasma	
The calibration curve was prepared in advance as pools of each standard point which were aliquotted into separate tubes and stored at -70 °C. The individual tubes were thawed as needed and aliquotted on the day of analysis. The calibrator pools were not used beyond their established stability.		
Sample Storage Stability		
First Sample Collected to Last Sample Extracted (Theoretical Maximum)	64 days	
Demonstrated Storage Stability	392 days at -70 °C	
Stability Data Reference	(b) (4) 13-225Add1 [11.4]	
Samples Collected and Analyzed within Stability Limits	Yes	
Incurred Sample Reanalysis (ISR)		
Incurred sample reanalysis samples were assayed in singlet in three analytical runs.		
Samples Meeting Acceptance Criteria for Budesonide	223 out of 281 samples (79.4%)	
Incurred Sample Reanalysis was Acceptable for Budesonide	Yes	

For the incurred sample reanalysis to be acceptable, a minimum of 67% of the repeat values (repeat value minus original value) for all analytes must be within ± 20% of the average of the original and repeat values. During incurred sample reanalysis (ISR) for all

three analytes, multiple samples demonstrated a relative % difference of >50% when compared to their original results. The Applicant reviewed the raw data and analysis history and there were no documented analytical issues or significant analytical abnormalities in the original or ISR runs to explain the observed differences. However, the overall ISR results for all analytes still met the acceptance criteria with a passing rate of >79% (79.4%, 88.1%, and 92.0% for budesonide, formoterol, and glycopyrrolate, respectively) and no impact is expected on the quality of the data or the integrity of the study. The bioanalytical report and method validation are acceptable.

Overall Assessment:

Overall, although the aforementioned BA studies failed to meet the BE acceptance criteria, the purpose of these studies was to evaluate the effect of the fixed-dose combination formulation on the PK of each individual component compared to the PK of the respective mono-products. The Applicant did not intend to achieve comparable PK as those of the respective mono-products. After consulting with *the Division of Pulmonary, Allergy, and Rheumatology Products*, it was decided that these failed BA studies do not affect the approvability of this NDA submission.

19. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Reviewer's Assessment:

There is no concern from Biopharmaceutics perspective.

**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACUTICS**

Reviewer's Assessment and Signature:

From the Biopharmaceutics perspective, NDA 208294 is recommended for approval.

Biopharmaceutics Primary Reviewer: Peng (Vincent) Duan, Ph.D.
Mar 15, 2016

Secondary Review Comments and Concurrence:

I have reviewed the Biopharmaceutics assessment, and I concur with the approval recommendation.

Kelly M. Kitchens, Ph.D.
Acting Quality Assessment Lead
Division of Biopharmaceutics Branch II
March 16, 2016

ASSESSMENT OF MICROBIOLOGY

Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

The following information is provided for drug substance: The subject drug product is composed of the following two active drug substances:

- Glycopyrronium bromide
- Formoterol Fumarate

Note to reviewer. The applicant has provided DMF for both the drug substances. The final drug product specification has appropriate microbial limits. Hence, the manufacture of these (b) (4) powders is not reviewed here.

Description of drug product – (3.2.P.1-description-composition.pdf, page 1/3)

Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI) is a fixed-dose combination product containing glycopyrronium (GP) and formoterol fumarate (FF). GFF MDI is formulated as a suspension with micronized glycopyrronium bromide and micronized formoterol fumarate co-suspended with a porous particle excipient in a hydrofluoroalkane (HFA) propellant. The formulation is contained within a (b) (4) aluminum can fitted with a metering valve, a white plastic actuator, an orange plastic dust cap, and a can-top dose indicator. The product is foil overwrapped with desiccant.

The strength of the GFF MDI product is 7.2 µg GP and 4.8 µg FF per actuation. A dose consists of two actuations from the inhaler, corresponding to 14.4 µg GP and 9.6 µg FF per dose, yielding total daily doses of 28.8 µg GP and 19.2 µg FF.

Table -Drug product composition (Reproduced from submission- 3.2.P.1-description-composition.pdf, page 3/3)

Component	Manufacturing Concentration (% w/w)	Quantity per canister ¹	Metered dose (ex-valve) ²	Delivered dose (ex-actuator)	Function
Glycopyrronium Bromide	(b) (4)	(b) (4)	8.32 µg ³	7.20 µg ³	Active ingredient

micronized					
Formoterol Fumarate micronized		(b) (4)	5.55 µg	4.80 µg	Active ingredient
Porous Particles				(b) (4)	Co suspending agent
HFA-134a					Pronellant (b) (4)

Formulation overages include drug overages of (b) (4)% to account for losses to the valve and actuator upon actuation.

³Metered and delivered dose are expressed as the active moiety (i.e. glycopyrronium)

• **Description of container closure system –**

(2.3.P.7- Container closure system; page 1/2)

The container-closure system (CCS) used for GFF MDI consists of a (b) (4) aluminum can sealed (b) (4)

Collectively the can and valve assembly is referred to as the canister. A dose indicator is attached via a label to the top of the canister and the canister/dose indicator assembly is fitted with a (b) (4) actuator and dust cap. A schematic drawing of the GFF MDI is provided. Each MDI is individually wrapped in a foil laminate pouch containing desiccant to protect the MDI from moisture ingress on storage and during transit.

-Acceptable-

Pharmaceutical Development

Microbiological Attributes

- Container-Closure and Package integrity: Not applicable
- Antimicrobial testing: Not applicable
- Justification for not having a microbial limit specification for a non-sterile drug product – This non-sterile product has an adequate microbial limit specification.

-Acceptable-

Manufacture

Manufacturers (3.2.P.3.1-manufacturers-dp.pdf)

Manufacturing, quality control and stability testing of micronized glycopyrronium bromide will be performed at the following site:

Pearl Therapeutics, Inc.
200 Cardinal Way
Redwood City, CA-94063

Manufacture and quality control of filled canisters:

Aventis Pharma Ltd
72 London Road
Holmes Chapel, Cheshire, CW4 8BE, UK

AstraZeneca Dunkerque Production (AZDP)

Microbial limits:

Test	Acceptance Criteria	Analytical Procedure
Microbiology	Total aerobic microbial count (TAMC)	NMT ^{(b) (4)} CFU/can
	Total combined yeast/molds count (TYMC)	NMT ^{(b) (4)} CFU/can
	Bile tolerant Gram-negative bacteria	Absence/can
	<i>P. aeruginosa</i>	Absence/can
	<i>S. aureus</i>	Absence/can
		USP<61> and USP<62>
		USP<1111>

Batch Analysis

Test	Acceptance criteria	3H015A March 2013	3H023A June 2013	3H024A June 2013
Microbial limit test (USP<61> and USP<62>)	Total aerobic count: NMT 200CFU/canister	< ^{(b) (4)} CFU/canister	< ^{(b) (4)} CFU/canister	< ^{(b) (4)} CFU/canister
	Total yeast and mold count: NMT20CFU/canister	< ^{(b) (4)} CFU/canister	< ^{(b) (4)} CFU/canister	< ^{(b) (4)} CFU/canister
	Absence of indicator pathogens: <i>P. aeruginosa</i> <i>S. aureus</i> Bile-tolerant gram negative bacteria	^{(b) (4)} canister	^{(b) (4)} canister	^{(b) (4)} canister

Analytical Procedures

- Endotoxin- Not applicable
- Sterility- Not applicable
- Microbial Limits (3.2.P.2.5-pharm-dev-micro-attributes.pdf)

USP<61> and USP<62>

A microbial challenge study has been performed to assess the ability of a range of microorganisms to grow in a suspension of porous particles in HFA-134a propellant (referred as Placebo MDI). The microbial challenge comprised gram-positive and negative aerobic bacteria, fungi (mold species), anaerobic bacteria, bacterial spores and species typical of an MDI production contribution (a species typical of skin-borne contamination and a species typical of facilities contamination). Early comparison studies demonstrated that GFF MDI presents equal or greater inhibitory properties than Placebo MDI to microbial growth.

Validation of microbial test:

The microorganisms were intentionally inoculated into 20 empty canisters that were then crimped closed with a valve. Placebo MDI formulations containing porous particles in HFA-134a were transferred through the valve into the canisters. The inoculated canisters were stored at 20-25°C for up to 28 days. Three canisters from each species were tested on the day of fill (day 0), 2 days post fill, and 28 days post fill. For *Bacillus subtilis* spores 3 canisters were tested at 14 days also, since a slower rate of decline was expected.

The number of CFU per canister was evaluated and the log reductions in populations calculated. Results are provided in table below.

Microbiological recovery from porous particles in HFA-134a

Species (Source)	Time point (day)	Mean CFU/canister	Mean log reduction from spike
<i>Pseudomonas aeruginosa</i> (Water-borne contamination)	Spike	1070	-
	0	20	1.77
	2	0	3.03
	28	0	3.03
<i>Clostridia sporogenes</i> (Anaerobic contamination)	Spike	500	-
	0	607	-0.08
	2	277	0.26
	28	0	2.70
<i>Bacillus cereus</i> (Facility contamination)	Spike	700	-
	0	527	0.17
	2	170	0.62
	28	7	2.18
<i>Aspergillus brasiliensis</i> (Mold contamination)	Spike	490	-
	0	550	-0.05
	2	143	0.54
	28	0	2.69
<i>Bacillus subtilis</i> (Spore contamination)	Spike	5700	-
	0	3227	0.28
	2	3543	0.21
	14	4200	0.14
	28	3767	0.18
<i>Candida albicans</i> (Yeast contamination)	Spike	1980	-
	0	213	0.98
	2	0	3.30
	28	0	3.30
<i>Escherichia coli</i> (USP <1111> objectionable organism)	Spike	600	-
	0	13	1.68
	2	0	2.78
	28	0	2.78
<i>Staphylococcus aureus</i> (USP <1111> objectionable organism)	Spike	2000	-
	0	1620	0.09
	2	0	3.30
	28	0	3.30

Species (Source)	Time point (day)	Mean CFU/canister	Mean log reduction from spike
<i>Staphylococcus epidermidis</i> (Skin-borne contamination)	Spike	870	-
	0	637	0.14
	2	200	1.41
	28	0	2.94

The study demonstrated a decrease in the average number of microorganisms per canister over a 28 day period. For the *B. subtilis* study where samples were spiked with endospores, the initial reduction was followed by steady state of population (no increase more than 0.5 log10). As per the applicant, these results collectively indicate that formulations containing porous particles in HFA-134a present a hostile environment for microorganisms, as such microbial proliferation is not expected over the recommended shelf life.

Container Closure System

See above under 'description of container closure system'. There is detailed information on the inhaler presented in this application but the information is not relevant to this product quality microbiology review.

Stability

Stability Summary and conclusion

The release and stability specifications are identical and are described under 'specification' section above. Microbial Limits (valve down of container) will be assessed at 6, 12, 18, 24, and 36 months under 25°C/60% RH incubation conditions in an inverted position.

Post-Approval Stability Protocol and Stability Commitment

First three commercial batches will be placed on long-term stability studies. The applicant states that 'based on the microbiological attributes, microbiological testing will not be performed for routine commercial GFF MDI release of the drug product. Microbial testing will be carried out on a minimum of one batch of product per year, as per ICH Q6A guidelines'.

Note to reviewer: The reviewer notes that ICH Q6A was referenced for the proposed testing on a minimum of one batch of product/year and that microbial testing will not be performed at release during routine production. Upon discussion with Bryan S. Riley, Microbiology Branch Chief (Acting), DMA/OPF/CDER, the applicant's Post-Approval Stability Protocol and Stability Commitment were concluded acceptable based on the following conclusions from the information provided in this NDA submission:

- The Drug product composition (b) (4) and there is no risk for microbial proliferation during manufacture of the (b) (4)
- The applicant has provided adequate microbial limit specification (USP <61> and USP <62> were referenced; acceptance criteria were indicated as: Total aerobic count: NMT

(b) (4) CFU/mg; Total yeast and mold count: NMT (b) (4) CFU/mg; absence of indicator pathogens: *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and bile tolerant Gram negative bacteria; it is indicated that Bile-tolerant Gram negative bacteria test conducted in accordance with USP <1111>) for at least one of the drug substances/API, Formoterol Fumarate. Batch Analyses tables for 3 NDA stability batches and 3 commercial CCS stability batches for the micronized drug substance, Formoterol Fumarate indicate that all the API batches had acceptable results and the proposed microbial limits specifications were met.

- In addition, the applicant has provided adequate validation data for microbial limits on the finished drug product. Based on these studies, the applicant indicated that both the drug product and the HFA-134a propellant inhibit microbial growth.

Stability Data

Batches 3H015A, 3H023A, 3H024A, 25°C/60%RH at following time-points: initial, 6 months, 12 months had TAMC < (b) (4) CFU/can, TYMC: < (b) (4) CFU/can (acceptance criteria: TAMC: (b) (4) CFU/can, TYMA: (b) (4) CFU/can). *P. aeruginosa*, *S. aureus*, bile tolerant gram-negative bacteria were absent.

-Acceptable-

Executed Batch Record (3.2.P.5.4-batch-analysis-dp.pdf, page 12/12)

Executed batch records were provided for the three primary stability batches.

(b) (4)

PACKAGE INSERT

There are no product quality microbiology concerns with the proposed package insert.

-Acceptable-

Applicant's Response:

Reviewer's Assessment: The information provided in support of drug product quality microbiology for NDA 208294 is acceptable.

2.3.P.7 Container/Closure System

20. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Reviewer's Assessment: Please see # 40 above.

A APPENDICES**A.2 Adventitious Agents Safety Evaluation**

21. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Reviewer's Assessment: No materials are obtained from animal sources.

22. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment: NA

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: There were no quality microbiology deficiencies identified in the information provided. The application is recommended for approval from a quality microbiology perspective.

Reviewer's Signature

Nutan Mytle, Ph.D.

Microbiology Reviewer

Branch II

Division of Microbiology Assessment/OPF

2/22/2016

Secondary Review Comments and Concurrence:

Nandini Bhattacharya, Ph.D.

DMA Branch II QAL (Acting)

2.22.2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

23. Is the applicant's claim for categorical exclusion acceptable?

Yes

24. Is the applicant's Environmental Assessment adequate for approval of the application? N/A

Reviewer's Assessment: ACCEPTABLE

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

Craig Bertha 06-JUL-2016

After consultation with the EA review team, it was concluded that this new indication would not be expected to significantly increase the use of these two drugs, and the applicant's claim of categorical exclusion as per 21 CFR 25.31(b) is acceptable.

Secondary Review Comments and Concurrence:

N/A

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert (April 4, 2016 amendment)

(Proposed text in italics)

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	<i>BEVESPI AEROSPHERE™ (glycopyrrolate and formoterol fumarate) inhalation (b) (4) for oral inhalation use</i>	ACCEPTABLE
Dosage form, route of administration	<i>inhalation aerosol, for oral inhalation use</i>	ACCEPTABLE
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	<i>Inhalation aerosol: Pressurized metered dose inhaler containing a combination of glycopyrrolate (9 mcg) and formoterol fumarate (4.8 mcg) as an inhalation aerosol.</i> <i>Two inhalations equal one dose.</i>	ACCEPTABLE

Conclusion: INADEQUATE See above

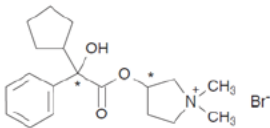
(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	<i>pressurized metered dose inhaler</i>	ACCEPTABLE
Strengths:	<i>delivers 9 mcg of glycopyrrolate and 4.8 mcg of formoterol fumarate per inhalation</i>	ACCEPTABLE
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	<i>The canister has an attached dose indicator and is supplied with a white plastic actuator with an orange dust cap.</i>	ACCEPTABLE

Conclusion: INADEQUATE See above

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	BEVESPI AEROSPHERE (glycopyrrolate and formoterol fumarate)	ACCEPTABLE
Dosage form and route of administration	pressurized metered-dose inhaler	ACCEPTABLE
Active moiety expression of strength	9 µg of glycopyrrolate (equivalent to 7.2 µg of glycopyrronium) and 4.8 µg of formoterol fumarate from the actuator	See discussion below ACCEPTABLE
Inactive ingredient information	Porous particles (comprised of the phospholipid, 1,2- Distearoyl-sn-Glycero-3-Phosphocholine (DSPC), and calcium chloride) and HFA 134a	DSPC and HFA-134a are non-compendial ACCEPTABLE
Chemical name, structural formula, molecular weight	Glycopyrrolate (b) (4)  398.33 Formoterol fumarate N-[2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino] ethyl]phenyl] formamide, (E)-2-butenedioate dihydrate 840.91	Note that, although the structure captures the chiral centers, the name should conform to the USAN. COMMENT: Change the chemical name of glycopyrrolate to the USAN, (RS)-[3-(SR)-Hydroxy-1,1-dimethyl pyrrolidinium bromide] α-cyclopentylmandelate
Other important chemical or physical properties (such as pKa, solubility, or pH)	Glycopyrrolate is a powder that is freely soluble in water. Formoterol fumarate is a powder that is slightly soluble in water	ACCEPTABLE

The applicant includes the following information in the Description section

"After priming each actuation of the inhaler meters 10.4 µg of glycopyrrolate (equivalent to 8.3 µg of glycopyrronium) and 5.5 µg of formoterol fumarate from the valve which delivers 9 µg of glycopyrrolate (equivalent to 7.2 µg of glycopyrronium) and 4.8 µg of formoterol fumarate from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system.

Priming BEVESPI AEROSPHERE is essential to ensure appropriate drug content in each actuation. Prime BEVESPI AEROSPHERE before using for the first time. To prime BEVESPI AEROSPHERE, release 4 sprays into the air away from the face, shaking well before each spray.

If the product is not used for more than 7 days re-prime the device. To re-prime BEVESPI AEROSPHERE, release 2 sprays into the air away from the face, shaking well before each spray."

ACCEPTABLE

Overall Conclusion: INADEQUATE See above

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	<i>BEVESPI AEROSPHERE Inhalation Aerosol is supplied as a pressurized aluminum canister with an attached dose indicator, a white plastic actuator and mouthpiece, and an orange dust cap. Each 120 inhalation canister has a net fill weight of 10.7 grams. Each canister is packaged in a foil pouch with desiccant sachet and is placed into a carton. Each carton contains one canister and a Medication Guide (NDC 0310- (b) (4))</i>	ACCEPTABLE
Special handling (e.g., protect from light, do not freeze)	<i>The correct amount of medication in each inhalation cannot be assured after the label number of inhalations from the canister have been used, when the dose indicator display window shows zero, even though the canister may not feel completely empty. BEVESPI AEROSPHERE should be discarded when the dose indicator display window shows zero or 3 months after removal from the foil pouch, whichever comes first. Never immerse the canister into water to determine the amount remaining in the canister ("float test").</i> <i>For best results, the canister should be at room temperature before use. Shake well before using. Keep out of reach of children.</i> CONTENTS UNDER PRESSURE <i>Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 49°C (120°F) may cause bursting. Never throw canister into fire or incinerator. Avoid spraying in eyes.</i>	ACCEPTABLE
Storage conditions	<i>Store at controlled room temperature 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP].</i>	ACCEPTABLE

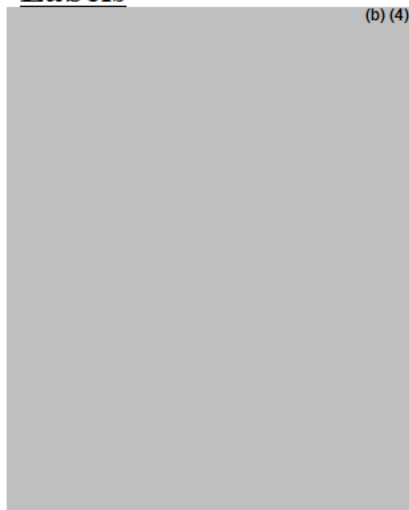
Conclusion: INADEQUATE See above

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	<i>Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850</i> <i>By: Aventis Pharma LTD, Holmes Chapel CW48BE, United Kingdom</i>	ACCEPTABLE

Conclusion:

2. Labels



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	No comments	ACCEPTABLE
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Present	
Net contents (21 CFR 201.51(a))	120 inhalations	
Lot number per 21 CFR 201.18	N/A	
Expiration date per 21 CFR 201.17	N/A	
"Rx only" statement per 21 CFR 201.100(b)(1)	Present	
Storage (not required)	N/A	
NDC number	No comments	
Bar Code per 21 CFR 201.25(c)(2)**	N/A	
Name of manufacturer/distributor	N/A	
Others	N/A	

ACCEPTABLE

Conclusion: ACCEPTABLE

(b) (4)



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	No comments	ACCEPTABLE
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	<i>Dosage : 2 inhalations twice daily. Warning : Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store at temperature above 120°F. Keep out of the reach of children. Contents : Each carton contains one canister. Net fill weight 10.7 grams providing 120 inhalations. Each actuation delivers 9 mcg of glycopyrrolate and 4.8 mcg of formoterol fumarate. Inactive ingredients include 1,2-distearoyl-sn-glycero- 3-phosphocholine (DSPC), calcium chloride and HFA 134a.</i>	ACCEPTABLE
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
Name of all inactive ingredients (except for oral drugs);		
"Rx only" statement per 21 CFR 201.100(b)(1)		
Storage Conditions		
NDC number		
Bar Code per 21 CFR 201.25(c)(2)**		
Name of manufacturer/distributor	<i>"Mfd. for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850 By: Aventis Pharma LTD, Holmes Chapel CW48BE, United Kingdom Product of UK"</i>	
"See package insert for dosage information" (21 CFR 201.55)	No comments	
"Keep out of reach of children" (optional for Rx, required for OTC)		
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))		

Conclusion: INADEQUATE See comments

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

OVERALL ASSESSMENT AND SIGNATURES: LABELING**Reviewer's Assessment and Signature:**

Signed: Arthur B. Shaw, Ph.D.

Secondary Review Comments and Concurrence:

I concur.
Craig M. Bertha
25-APR-2016

II. List of Deficiencies To Be Communicated N/A

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

DP attribute/ CQA	Factors that can impact the CQA ²	O ³	S ^{5,4}	D ⁵	FMECA RPN #	Comments on Risks and Mitigation
Delivered Dose Uniformity (DDU for glycopyrrolate and formoterol fumarate)	- Suspension formulation inhomogeneity - Low formulation assay (e.g. degradation of actives, loss of active(s) to canister surface) - Lower than target fill of canisters (insufficient overfill) - Loss of actives to manufacturing equipment - Device malfunction (e.g., valve blow-by, actuator clogging, leakage) - Failure of protective packaging	2	3	3	18	(b) (4)

² Patient mis-use can impact performance of device but human factors are beyond scope of CMC evaluation.

³ O = Probability of Occurrence; S = Severity of Effect; D = Detectability

⁴ Severity of effect can only be estimated; input from clinical or pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs; also, this is a topically applied drug for local action so correlation of *in vitro* parameters to *in vivo* behavior would be difficult to estimate.

						(b) (4)
Aerodynamic Particle Size Distribution (APSD)	- Mass balance - All of the risks to DDU above are also risks to total mass balance of APSD - APSD profile - Input particle size of actives (b) (4) - Hygroscopicity of	2	3	4	24	

	actives ○ (b) (4) ○ Failure of protective packaging leading to increase in moisture content						(b) (4)
(b) (4)	• (b) (4) • APIs and excipients, CCS components • Failure of protective packaging	2	3	4	24		

7/6/15

**OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW**

Application #: 208294	Submission Type: 3	Established/Proper Name: Glycopyrrolate/Formoterol Fumarate (GFF)
Applicant: Pearl Therapeutics, Inc.	Letter Date: 25-JUN-2015	Dosage Form: inhalation aerosol (or metered dose inhaler or MDI)
Chemical Type: non- NMEs	Stamp Date: 25-JUN-2015	Strength: 9.0 mcg Glycopyrrolate¹ and 4.8 mcg Formoterol fumarate/actuation

Pearl's combination drug/combination product (GFF MDI) is an inhalation aerosol with a suspension formulation of glycopyrrolate (antimuscarinic) and formoterol fumarate or FF (beta-agonist) in HFA-134a. This suspension also contains porous particles (co-suspending agent) (b) (4) a mixture of 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC) and calcium chloride (CaCl₂) (b) (4)

The formulation of GFF MDI is contained in a (b) (4) aluminum canister fitted with a crimped-on metering valve, plastic actuator/dust cap and a top of canister mounted dose indicator. The drug product also includes protective packaging in the form of a foil laminate with enclosed desiccant. The proposed proprietary name of the drug product is BEVESPI AEROSPHERE and the proposed indication is "for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)." The drug delivers 9.0 mcg of glycopyrrolate and 4.8 mcg of formoterol fumarate from the mouthpiece/actuation. The dosage is 2 inhalations twice daily (BID), or 36.0 mcg of glycopyrrolate and 19.2 mcg of formoterol fumarate per day. The applicant proposes a 24 month shelf life for the drug product and a 3 month in-use period (after removal of protective packaging). It is important to note that when the drug product is outside of the protective packaging, it takes up moisture and at some point after 3 months, the moisture content reaches a point at which there is a negative impact on the delivered dose uniformity or DDU (increased variability). Thus, this quality aspect deserves close attention and evaluation.

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	X		

¹ 9.0 mcg glycopyrrolate (glycopyrronium bromide, a quaternary ammonium salt) is equivalent to 7.2 mcg of glycopyrronium cation.

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?		X	

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ²	☐	X	
2.	Botanical ²	☐	X	
3.	Naturally-derived Product	☐	X	
4.	Narrow Therapeutic Index Drug	☐	X	
5.	PET Drug	☐	X	
6.	PEPFAR Drug	☐	X	
7.	Sterile Drug Product	☐	X	
8.	Transdermal ²	☐	X	
9.	Pediatric form/dose ²	☐	X	
10.	Locally acting drug ²	X	☐	
11.	Lyophilized product ²	☐	X	
12.	First generic ²	☐	X	
13.	Solid dispersion product ²	☐	X	
14.	Oral disintegrating tablet ²	☐	X	
15.	Modified release product ²	☐	X	
16.	Liposome product ²	☐	X	
17.	Biosimilar product ²	☐	X	
18.	Combination Product	X	☐	
19.	Other	X	☐	Also a combination product

² Contact Office of Testing and Research for review team considerations

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

Regulatory Considerations				
20.	USAN Name Assigned	X	☐	For both glycopyrrolate and formoterol fumarate
21.	End of Phase II (21-DEC-2012)/Pre-NDA Agreements (19-JAN-2015) for IND 107739	X	☐	Pre-NDA: - There was an agreement with the applicant that the porous particles were not considered to be a novel excipient and information for CTD P.4 section would be submitted separately in a DMF. - Drug substance specifications and batch analyses are to be included in S sections of modules 2&3. - Data would be included to support changes (b) (4) from phase III to commercial drug product. - Stability data for micronized glycopyrrolate will be included to support a retest period. (b) (4) "Glycopyrrolate" would be the established name used for the glycopyrrolate drug. EoP2: - We agreed to a supplier change and micronization process change for the glycopyrrolate for the phase III drug product. (b) (4) - The Agency provided the applicant with suggested revisions to the drug substance and porous particle (b) (4) specifications (mainly for missing tests).
22.	SPOTS (Special Products On-line Tracking System)	☐	X	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	☐	X	
24.	Comparability Protocol(s) ³	X	☐	See (b) (4) C.2 below.
25.	Other	☐	X	

³ Contact Post Marketing Assessment staff for review team considerations

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

Quality Considerations					
26.	Drug Substance Overage		X	☐	The phase III drug product used a (b)(4)% overage of the drug substances to account for drug lost to the manufacturing equipment surfaces. This is distinct from expected loss of drug to the valve and actuator components upon actuation (about (b)(4)% CCS deposition), and the additional amount of formulation or overfill required to assure the sufficient number of actuations can be obtained.
27.	Design Space	Formulation	☐	X	
28.		Process	☐	X	
29.		Analytical Methods	☐	X	
30.		Other	☐	X	
31.	Real Time Release Testing (RTRT)		☐	X	
32.	Parametric Release in lieu of Sterility Testing		☐	☐	N/A
33.	Alternative Microbiological Test Methods		☐	X	
34.	Process Analytical Technology ²		☐	X	
35.	Non-compendial Analytical	Drug Product	X	☐	
36.	Procedures and/or	Excipients	X	☐	
37.	specifications	Microbial	☐	X	
38.	Unique analytical methodology ²		☐	X	
39.	Excipients of Human or Animal Origin		☐	X	Refer to DMF (b)(4) separately for information regarding the porous particles; Refer to DMF (b)(4) for information regarding the HFA-134a propellant
40.	Novel Excipients		☐	X	The Agency agreed at the Pre-NDA meeting that the porous particles were not considered a novel excipient
41.	Nanomaterials ²		☐	X	
42.	Hold Times Exceeding 30 Days		☐	X	(b)(4)
43.	Genotoxic Impurities or Structural Alerts		X	☐	Refer separately to DMF (b)(4) for FF and DMF (b)(4) for glycopyrrolate; an (b)(4) impurity for FF was mentioned in the toxicology summary in module 2.
44.	Continuous Manufacturing		☐	X	
45.	Other unique manufacturing process ²		☐	X	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	X	
47.	New delivery system or dosage form ²		☐	X	
48.	Novel BE study designs		☐	☐	
49.	New product design ²		X	☐	The use of the porous particles as a co-suspension agent for an MDI can

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

				be considered to be a new or novel design for an application that has been submitted as an NDA [past MDIs (b) (4)]
50.	Other	☐	☒	

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Pearl requests a categorical exclusion under 21 CFR 25.31(b) and 25.15(d). Waiver is not supported in the application with calculations of the expected (environmental) introduction concentrations of the two drugs, as a result of the increased use expected upon approval and marketing. James Laurenson of OPQ has indicated that we generally do not need to have these calculations, unless the compound is known to have estrogenic, androgenic, or thyroid activity (not the case here).
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ Drug Substance ☐ Drug Product ☐ Appendices ○ Facilities and Equipment ○ Adventitious Agents Safety Evaluation ○ Novel Excipients ☐ Regional Information ○ Executed Batch Records ○ Method Validation (MV) Package ○ Comparability Protocols	☐	☐	☒	Not necessary to review QOS if more detailed information in module 3 is reviewed. The QOS does not include summary information other than for drug substances and drug product.
FACILITY INFORMATION					

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

C. FILING CONSIDERATIONS					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ☐ Name of facility, ☐ Full address of facility including street, city, state, country ☐ FEI number for facility (if previously registered with FDA) ☐ Full name and title, telephone, fax number and email for on-site contact person. ☐ Is the manufacturing responsibility and function identified for each facility, and ☐ DMF number (if applicable)	X	☐	☐	There are nine (9) sites listed on the form 356h.
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ☐ Is a manufacturing schedule provided? ☐ Is the schedule feasible to conduct an inspection within the review cycle?	☐	X	☐	The Aventis site in Holmes Chapel, UK (b) (4) (b) (4) (b) (4) the AstraZeneca site in Dunkerque, France (b) (4) (b) (4) (considering the filing deadline, this is acceptable).
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☐	X	☐	There are sixteen (16) DMFs referenced by the applicant. Note that the evaluation of DMF (b) (4) will be the responsibility of the pharmacology/toxicology team. Not all DMF LOAs are from US based agents (DMFs (b) (4)).
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ general information ☐ manufacture ☐ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using	X	☐	☐	Formoterol fumarate information is mainly provided by reference to DMF (b) (4). Glycopyrrolate information is mainly provided by reference to DMF (b) (4). Although the applicant has complied with our request at the pre-NDA meeting, to include the drug substance specifications

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only ☐ characterization of drug substance ☐ control of drug substance ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ☐ reference standards or materials ☐ container closure system ☐ stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				and batch analyses, it is notable that no associated test methods are provided for these. As such, it is unclear how the applicant would meet the requirements of 21 CFR 211.84(d)(2).
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ Description and Composition of the Drug Product ☐ Pharmaceutical Development ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development ☐ Manufacture ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ☐ Control of Excipients ☐ Control of Drug Product ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	☐	X	☐	No associated test methods are provided for the HFA-134a propellant. As such, it is unclear how the applicant would meet the requirements of 21 CFR 211.84(d)(2) for this drug product component. As per Agency recommendations, stability batches were manufactured at 1/3rd commercial scale. A 24 month shelf life and 3 month in-use period are proposed. Long term stability data range from 15-18 months (both valve up and down orientations). For the MV package, the applicant lists samples that can be requested. Analytical methods and validation reports are provided in the package by

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

C. FILING CONSIDERATIONS					
	○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ☐ Reference Standards or Materials ☐ Container Closure System ○ Include data outlined in container closure guidance document ☐ Stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ☐ APPENDICES ☐ REGIONAL INFORMATION				hyperlink only. No dissolution testing is proposed.
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	X	The drug is for topical application to the lungs for local effect only.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	☐	☐	X	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☐	X	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	X	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	X	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility,	☐	☐	X	

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FILING REVIEW

C. FILING CONSIDERATIONS				
	stability, and dissolution data?			
REGIONAL INFORMATION AND APPENDICES				
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	X	☐
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	X	☐	☐
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ☐ facilities and equipment - o manufacturing flow; adjacent areas - o other products in facility - o equipment dedication, preparation, sterilization and storage - o procedures and design features to prevent contamination and cross-contamination ☐ adventitious agents safety evaluation (viral and non-viral) e.g.: - o avoidance and control procedures - o cell line qualification - o other materials of biological origin - o viral testing of unprocessed bulk - o viral clearance studies - o testing at appropriate stages of production ☐ novel excipients	☐	☐	X
17.	Are the following information available for Biotech Products: ☐ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: - o LAL instead of rabbit pyrogen - o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			X

ONDP Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

DP attribute/ CQA	Factors that can impact the CQA ⁴	O ⁵	S ^{5,6}	D ⁵	FMECA RPN #	Comment & considerations
Delivered Dose Uniformity (DDU for glycopyrrolate and formoterol fumarate)	- Suspension formulation inhomogeneity - Low formulation assay (e.g. degradation of actives, loss of active(s) to canister surface) - Lower than target fill of canisters (insufficient overfill) - Loss of actives to	2	3	4	24	(b) (4)

⁴ Patient mis-use can impact performance of device but human factors are beyond scope of CMC evaluation.

⁵ O = Probability of Occurrence; S = Severity of Effect; D = Detectability

⁶ Severity of effect can only be estimated; input from clinical or pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs; also, this is a topically applied drug for local action so correlation of *in vitro* parameters to *in vivo* behavior would be difficult to estimate.

ONDP Initial Quality Assessment (IQA) and Filing Review

For Pre-Marking Applications

	- manufacturing equipment • Device malfunction (e.g., valve blow-by, actuator clogging, leakage) • • Failure of protective packaging					(b) (4)
Aerodynamic Particle Size Distribution (APSD)	• Mass balance ○ All of the risks to DDU above are also risks to total mass balance of APSD • APSD profile ○ Input particle size of actives ○ (b) (4) ○ Hygroscopicity of actives ○ (b) (4)	2	3	4	24	

ONDP Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

	○ Failure of protective packaging leading to increase in moisture content						(b) (4)
(b) (4)	• (b) (4) APIs and excipients, CCS components • Failure of protective packaging	2	3	5	30		

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Craig M. Bertha, PhD
CMC Lead

Craig M. Bertha -S

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Julia Pinto, PhD
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