CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212122Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 212122
Review #1

Drug Name/Dosage Form	budesonide (BD)/glycopyrrolate or glycopyrronium bromide (GPBr)/formoterol fumarate (FF) or BGF
Strength	160/9.0/4.8 mcg/act BD/GPBr/FF
Route of Administration	oral inhalation
Rx/OTC Dispensed	Rx
Applicant	AstraZeneca (AZ) LP
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*30-NOV-2018*	*all*
Amendment	*16-JAN-2019*	*drug product/process*
Amendment	*28-FEB-2019*	*drug product*
Amendment	*31-MAY-2019*	*drug product/process*
Amendment	*05-JUN-2019*	*facilities*
Amendment	*15-AUG-2019*	*drug substance*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Soumya (Shomo) Mitra	Donna Christner
Drug Product	Renish Delvadia	Craig M. Bertha
Process	Ramesh Dandu	Yong Hu
Microbiology	Ramesh Dandu	Yong Hu
Facility	Ramesh Dandu	Yong Hu
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Florence Aisida/Grace Gnall	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
ORA Lead/CDRH OC	Emre Genca	
Environmental	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	10-JUN-2019	Reviewed by Dr. Soumya Mitra
	Type II			Adequate	25-JUL-2019	Reviewed by Dr. Soumya Mitra
	Type II			Adequate	21-MAY-2019	Reviewed by Dr. Soumya Mitra
	Type II			Adequate	02-AUG-2019	Reviewed by Dr. Soumya Mitra
	Type IV			Adequate	06-JAN-2016	Reviewed by Arthur Shaw
	Type IV			Adequate	17-FEB-2012	Reviewed by Dr. Xiaobin Shen
	Type III			Adequate	17-MAR-2009	Reviewed by Dr. Arthur Shaw
	Type III			Adequate	19-NOV-2011	Reviewed by Dr. Wendy Wilson-Lee
	Type III			Adequate	06-JAN-2016	Reviewed by Dr. Arthur Shaw
	Type III			Adequate	19-APR-2012	Reviewed by Dr. Raman Krishna
	Type III			Adequate	N/A	Refer to review of DMF 24105
	Type III			Adequate	N/A	Refer to review of DMF 24105
	Type III			Adequate	24-APR-2014	Reviewed by Dr. Markofsky Sheldon
	Type III			Adequate	21-OCT-2016	Reviewed by Dr. Gopalswamy Ramesh
	Type III			Adequate	24-OCT-2012	Reviewed by Dr. Klein Donald
	Type III			Adequate	13-OCT-2006	Reviewed by Dr. Schroeder Alan
	Type III			Adequate	07-APR-2016	Reviewed by Dr. Arthur Shaw
	Type III			Not reviewed		Sufficient information

			(b) (4)			provided in the application.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	118313	BGF MDI
IND	122166	BFF MDI
IND	107739	GFF MD
IND	121629	BD MDI
IND	101985	GPBr MDI
IND	105586	FF MDI
NDA	208294	Bevespi Aerosphere
NDA	21929	Symbicort

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/ Toxicology	N/A			
CDRH	Complete	No PAI required from the device perspective	05-MAR-2019	Emre Genca
Clinical	N/A			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

N/A – The application is recommended for **approval**. Note, however, that there are CMC-related label/labeling comments that will need to be addressed in the next review cycle regarding the potential need for equivalency strength statements.

II. Summary of Quality Assessments

A. Product Overview

The triple fixed-combination (21 CFR 300.50) and combination product [21 CFR 3.2(e)] from AZ is an inhalation aerosol that is formulated as a suspension of BD, GPBr, and FF active pharmaceutical ingredients (APIs), with proprietary porous particles (b) (4), and with HFA-134a propellant. There (b) (4) budesonide with 3 manufacturing sites, and the GPBr and FF each have single sources. The product is indicated for the (b) (4) maintenance treatment (b) (4) in patients with chronic obstructive pulmonary disease (COPD) (b) (4) The suspension formulation is contained within (b) (4) aluminum can fitted with a metering valve, a white plastic actuator, a grey plastic dust cap, and a top-mounted dose indicator. The product is foil overwrapped with desiccant (b) (4) (b) (4)

The metering valve delivers a nominal (b) (4) formulation volume upon actuation. There are three configurations for the drug product, which only differ in fill weight: 120 actuations (trade), (b) (4) and 28 actuations (for hospital use and as a physician sample). (b) (4) Each actuation from each presentation delivers 160 mcg BD, 9.0 mcg GPBr (equivalent to 7.2 mcg glycopyrronium cation), and 4.8 mcg FF (equivalent to (b) (4) mcg FF dihydrate and 4.1 mcg of formoterol base). The product is very similar to AZ's approved double fixed-combination drug product and combination product, Bevespi Aerosphere (GPBr/FF 9.0/4.8 mcg) Inhalation Aerosol of N208294. Specifically, the can, valve and actuator for BGF MDI are, for all intents and purposes, the same as those approved for use as part of Bevespi Aerosphere. In addition, the proposed 120 and 28

actuations Breztri Aerosphere canisters contain the same excipients (i.e., porous particles and HFA-134a), in the same amounts as in Bevespi Aerosphere 120 and 28 actuation canisters, respectively.

The drugs are not NMEs, are not considered by the applicant to be narrow-therapeutic, and are used for the treatment of COPD alone or in combination with other drugs. Manufacturing is similar to that used for Bevespi Aerosphere. The Critical in-process controls (IPCs) include (b) (4) The summary of changes made to the combination product *post* the phase III clinical studies (refer to attachment 1 of the P.2 pharmaceutical development section) were found to be of no consequence or were supported with *in vitro* data. Important drug product characterization studies were included in attachment 2 of P.2 to support labeling statements about usage.

A report on returned drug product from the clinical studies is included in attachment 4 of P.2. The Agency discussed the issue of actuator cleaning/occlusion at the 24-JUN-2017, meeting (under IND 118313). As a result, attachment 6 of P.2 includes a study where samples of the drug product are stored at 25°C/60%RH and 25°C/75%RH and are either subjected to weekly actuator cleaning or not. The data for product stored at higher humidity with no cleaning clearly showed more variable dose delivery, indicative of drug deposition on the actuator. This may be related to the high complaint rate reported (see attachment 4 of P.2). The Agency also agreed to accept bracketed stability data in terms of the product fill (b) (4) fill versions: 120, (b) (4) and 28 actuations/can), (b) (4) stablished by the two bracketing product fills (120 and 28 act/can). We agreed that if degradation products in the drug product at release are demonstrated to be consistent with the CoAs for the drug substances, degradation products may be controlled at the drug substance level for release of the drug product, with testing of the drug product occurring during annual maintenance (routine) stability. Note that although not specifically addressed for the IND 118313, (b) (4) The IQA for Bevespi Aerosphere (N208294) facilitated review of this application regarding the leachables and other parameters of the control strategy, due to the close similarity of these two combination products.

In order to comply with the requirements of 21 CFR 300.50, the Agency had asked the applicant to provide *in vitro* data demonstrating the comparable performance of the single, double, and triple fixed-combination combination products and acknowledged that these data would be reviewed with the NDA (see 17-JUL-2013, minutes for IND 118313). We asked that the applicant provide full aerodynamic particle size distribution (APSD) data both graphically and in a tabular fashion, stage-by-stage, to ease comparison (see the written responses of 11-APR-2014, for IND 118313). These comparative data

for BGF vs. GFF and BFF MDIs, BFF vs. BD and FF MDIs, and GFF vs. GPBr and FF MDIs, were found in see P.2.2.2 of IND 11831, P.2.2.2 of IND 122166, and P.2.2.5 of IND 107739, respectively. An evaluation of these data has concluded that there was sufficient comparability such that the clinical study results can be used to support the requirements of 21 CFR 300.50.

Comparability protocols were provided for review in the regional section of the application, for post-approval changes to canister coating, changes to provide a desiccated flow path, change to incorporate the counter from Symbicort inhalation aerosol. Also in this section was a summary of how the applicant is complying with the 21 CFR 820 device-related GMP regulations.

The initial risk assessment found that there was moderate risk for several of the drug product critical quality attributes (CQAs), including the delivered dose uniformity (DDU) and the aerodynamic particle size distribution (APSD), mainly for missing acceptance criteria and testing for component parameters that are likely related to the achievement of acceptable dosing performance. Also, there was little description supporting the applicant's statement that they manufacture and package the drug product in a sufficiently clean environment to assure it is "substantially free from foreign particles." However, the drug product specifications include tests and acceptance criteria for foreign particulate matter. In addition, due to the satisfactory GMP history for that site, and the close similarity of this drug product to the approved Bevespi Aerosphere product of NDA 208294, the risk was sufficiently low such that a pre-approval inspection was not deemed necessary for the drug product manufacturing site. Amendments to the application have mitigated the risks initially identified (see final risk assessment at end of review).

Proposed Indication(s) including Intended Patient Population	indicated for the (b) (4) (b) (4), maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD) (b) (4)
Duration of Treatment	Chronic
Maximum Daily Dose	320 mg budesonide, 18 mcg glycopyrrolate, and 9.6 mcg formoterol fumarate twice a day
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

The triple fixed-combination (21 CFR 300.50) and combination product [21 CFR 3.2(e)] from AZ inhalation aerosol is formulated as a suspension of BD, GPBr, and FF, none of which are new molecular entities. The applicant provides most of the information for BD, GPBr, and FF via references to supplier DMFs. Note that the applicant amended the application on 15-AUG-2019, to include the specification they apply when accepting FF from their supplier, as this was erroneously missing from the original application. Whereas the information supporting the FF and GPBr are now equivalent to what was approved for the applicant's previously approved double

combination Bevespi Aerosphere of NDA 208294 (both applications reference the same DMFs for these APIs), this triple combination inhalation aerosol adds BD, which is provided by two sources with 3 manufacturing sites (note that both GPBr and FF each have single sources). The drug substance review team confirms that BD from both sources have comparable quality and are adequate for use in formulating the drug product. A retest period of (b) (4) months for the BD is currently proposed and supported by stability data, however the applicant will continue the stability studies to potentially extend this period to (b) (4) months.

The application has provided the results of multiple product development studies to demonstrate chemical and physical stability, and robustness of Breztri Aerosphere, and have provided information to support labeling statements and patient instructions for use. The Applicant has provided 24 months of long-term, 12 months intermediate, and 6 months of accelerated stability data for three primary stability batches each of 120 and 28 actuations configuration, along with the supportive in-use and leachables stability data. The primary stability batches of the 120-actuation configuration were also used in the Phase III clinical trials. Overall, the stability data submitted by the applicant supports the proposed shelf-life of 24 months for all product configurations. The Applicant has adequately demonstrated *in vitro* comparability of the proposed triple API combination product with the respective dual-therapy products used in the clinical studies (GFF and BFF). Phase 3 clinical studies were conducted using drug product with actuator spray orifice diameters (SOD) centered in the range of (b) (4) (b) (4). However, afterwards, the Applicant narrowed the SOD acceptance criterion to a range of (b) (4). The narrower range results in a lower propensity for drug/excipient deposition in the orifice, which can lead to drug product performance issues if patients fail to follow the instructions for weekly cleaning. The Applicant has adequately bridged the change in the SOD acceptance criterion with *in vitro* performance data. During the review cycle, three information requests (IR) were sent to the Applicant, mainly for stability data summaries, specification justification, and for modification of the proposed comparability protocols. The applicant responded adequately and all drug product-related issues are resolved.

The manufacturing process for the triple combination inhalation aerosol is analogous to what was approved for Bevespi Aerosphere under NDA 208294, with the exception of the additional API (BD). In summary, the manufacturing process involves (b) (4) (b) (4)

(b) (4)

There are twelve manufacturing/testing sites supporting the application. No pre-approval inspections were considered necessary and all sites are found to be acceptable based on previous compliance histories.

C. Special Product Quality Labeling Recommendations (NDA only)

Although it is clear that the Agency salt nomenclature guidance recommends that the applicant add strength equivalency statements to the labels for formoterol fumarate, it is at present unclear if this approach is needed for the quaternary salt glycopyrrolate.

D. Final Risk Assessment (see Attachment)

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Since the current submission will be issued CR due to clinical deficiencies, the final assessment of label/labelling, including strength per MaPP 5021/salt nomenclature guidance, will be done during the next review cycle

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRADENAME AEROSPHERE	Replace with accepted proprietary name.
Established name(s)	(budesonide, glycopyrrolate, and formoterol fumarate) inhalation aerosol	Acceptable
Route(s) of administration	for oral inhalation use	Acceptabale
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Inhalation aerosol: Pressurized metered dose inhaler containing a combination of budesonide (160 mcg), glycopyrrolate (9 mcg), and formoterol fumarate (4.8 mcg) (b) (4) (b) (4) inhalation . (b) (4)	Acceptable
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	TRADENAME AEROSPHERE (b) (4) canister has an attached dose indicator, which indicates how many inhalations remain. The dose indicator display will move after every tenth actuation. When nearing the end of the usable inhalations, the color behind the number in the dose indicator display window changes to red. TRADENAME AEROSPHERE should be discarded when the dose indicator display window shows zero. (b) (4) Prime TRADENAME AEROSPHERE before using for the first time. (b) (4) prime TRADENAME AEROSPHERE, release 4 sprays into the air away from the face, shaking well before each spray. (b) (4) the inhaler has not been used for more than 7 days, (b) (4) is dropped, or after weekly cleaning (b) (4) prime (b) (4) release 2 sprays into the air away from the face, shaking well before each spray.	Acceptable

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	a pressurized metered dose inhaler	Acceptable
Strength(s) in metric system	combination of 160 mcg budesonide, 9 mcg glycopyrrolate, and 4.8 mcg formoterol fumarate per inhalation (b) (4) (b) (4)	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		Strength listed for glycopyrrolate and formoterol fumarate are consistent with Bevespi.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	The canister has an attached dose indicator and is supplied with a white plastic actuator with a light grey dust cap.	Acceptable
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

APPEARS THIS WAY ON ORIGINAL

Section 11 (DESCRIPTION)Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRADENAME AEROSPHERE (budesonide, glycopyrrolate and formoterol fumarate) Inhalation Aerosol	Acceptable
Dosage form(s) and route(s) of administration	Inhalation Aerosol ; for oral inhalation	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	After priming, each actuation of the inhaler meters 182 mcg of budesonide, 10.4 mcg of glycopyrrolate (equivalent to 8.2 mcg of glycopyrronium), and 5.5 mcg of formoterol fumarate from the valve which delivers 160 mcg of budesonide, 9 mcg of glycopyrrolate (equivalent to 7.2 mcg of glycopyrronium), and 4.8 mcg of formoterol fumarate from the actuator.	Will be evaluated in the next review cycle.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	TRADENAME AEROSPHERE also contains porous particles that form a cosuspension with the drug crystals. The porous particles are comprised of the phospholipid, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and calcium chloride. Porous particles and HFA 134a are excipients in the formulation.	Acceptable
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	

Statement of being sterile (if applicable)		
Pharmacological/ therapeutic class	budesonide (an inhaled corticosteroid), micronized glycopyrrolate (an anticholinergic), and micronized formoterol fumarate (a long-acting beta2-adrenergic agonist)	Accepable

Chemical name, structural formula, molecular weight	Budesonide is a corticosteroid with the following chemical name: (RS)-11β, 16α, 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is a white to off-white, powder which is practically insoluble in water. The molecular formula is $C_{25}H_{34}O_6$ and the molecular weight is 430.5. Budesonide contains (b) (4) chiral center and is (b) (4) mixture] of the two epimers (22R and 22S). Glycopyrrolate is a quaternary ammonium salt with the following chemical name: (RS)-[3-(SR)-Hydroxy-1,1-dimethylpyrrolidinium bromide] α-cyclopentylmandelate. Glycopyrrolate is a powder that is freely soluble in water. The molecular formula is $C_{19}H_{28}BrNO_3$, and the molecular weight is 398.33 g/mol. Glycopyrrolate contains two chiral centers (b) (4) and is a racemate of a 1:1 mixture of the R,S and S,R diastereomers. The active moiety, glycopyrronium, is the positively charged ion of glycopyrrolate. Formoterol fumarate has the chemical name N-[2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1- methylethyl]-amino] ethyl]phenyl] formamide, (E)-2-butenedioate dihydrate. Formoterol fumarate is a powder that is slightly soluble in water. The molecular formula is $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$ and the molecular weight is 840.91 g/mol. Formoterol fumarate contains two chiral centers (b) (4)	Acceptable

	(b) (4) and consists of a single enantiomeric pair (a racemate of R,R and S,S).	
If radioactive, statement of important nuclear characteristics.		
Other important chemical or physical properties (such as pKa or pH)	TRADENAME AEROSPHERE is formulated as a hydrofluoroalkane (HFA 134a) propelled pressurized metered dose inhaler containing 28 or 120 inhalations. The canister has an attached dose indicator and is supplied with a white plastic actuator body and mouthpiece with a light grey dust cap. (b) (4)	Acceptable

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable		
Remove statements that may be misleading or promotional (e.g., "synthesized and developed	None	N/A

by Drug Company X," "structurally unique molecular entity"		

1.2.3 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	TRADENAME AEROSPHERE Inhalation Aerosol	Acceptable
Strength(s) in metric system	Not included	FF and GPBr consistent with Bevespi; Will be evaluated in the next review cycle.
Available units (e.g., bottles of 100 tablets)	Each 120-inhalation canister has a net fill weight of 10.7 grams (NDC 0310-4616-12) (b) (4) each 28-inhalation canister (institutional pack) has a net fill weight of 5.9 grams (NDC 0310-4616-39).	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	Acceptable
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	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. TRADENAME AEROSPHERE should be discarded when the dose indicator display window shows zero for 3 months (for the 120-inhalation canister) or 3 weeks (for the 28-inhalation canister) 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"). Shake well before using. Keep out of reach of children. (b) (4)	Acceptable
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	Each canister of TRADENAME AEROSPHERE is packaged in a foil pouch with desiccant sachet and is placed into a carton. Each carton contains one canister and Patient Information.	Acceptable
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	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].	Acceptable

Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”		
Include information about child-resistant packaging	Not Applicable	**N/A**

1.2.4 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	TRADENAME AEROSPHERE is a trademark of the AstraZeneca group of companies. © AstraZeneca 2018 Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850; Manufactured by: AstraZeneca Dunkerque Production (AZDP), Dunkerque France For more information, go to (b) (4)	Acceptable

2.0 PATIENT LABELING

The submitted information in the patient labeling, instruction for use are similar to Bevespi, except for additional of weekly cleaning instruction. The information is adequate from CMC perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Copy/paste or refer to a representative example of a proposed container)

Canister label

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence		Acceptable; Include approved tradename
Dosage strength	Included	Acceptable
Route of administration	Included	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not included	Will be evaluated in the next review cycle.
Net contents (e.g. tablet count)	Included	Acceptable
"Rx only" displayed on the principal display	Included	Acceptable
NDC number	Included; separate for each count format	Acceptable
Lot number and expiration date	Included	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Included	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Included	Acceptable

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Included	Acceptable
Medication Guide (if applicable)	Included	Acceptable
No text on Ferrule and Cap overseal	N.A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available		

Assessment of Carton and Container Labeling:

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Since the current submission will be issued CR due to clinical deficiencies, the final assessment of label/labelling including strength per MaPP 5021/salt nomenclature guidance will be done during the next review cycle.

Primary Labeling Assessor Name and Date: Renishkumar Delvadia, 08/19/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed): Craig Bertha, 08/19/2019

DOCUMENT HISTORY

Document History	
Author: Integrated Quality Assessment Team, and Don Henry.	
Clearance Statement: This document is sponsored by the Integrated Quality Assessment Team. Jorge Rondon (OPRO/OE), Don Henry (OPRP/OE), and the Integrated Quality Assessment Team have cleared this template for use.	This process (CDER OPQ Integrated Quality Assessment Template) will be assessed at the following intervals and changes to the work aid will be captured as needed: This process will be assessed approximately 150 days from date issued (February 1, 2019).
Version	**Summary of Changes** **Date Issued**
04	Content update 01/17/2017
05	10/15/2017 GDUFA II Drop-down option added
06	1/3/2019 1. The Previous template and assessment guide contained information relevant to both ANDA and NDA. The document is now separated into two documents for each application type. 2. Replaced distinct Process and Facilities chapters with the new integrated Manufacturing chapter. 3. Made content updates to NDA Labeling chapter. 4. Added Maximum Daily Dose (MDD) field.

Renishkumar Delvadia

Digitally signed by Renishkumar Delvadia
Date: 8/19/2019 09:40:34AM
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Craig Bertha

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Final Risk Assessment for BGF Inhalation Aerosol – NDA 212122

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	Lifecycle considerations or comments
Delivered Dose Uniformity (DDU for BD, GP, and FF)	• 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	4	3	4	48	(b) (4)	(b) (4)	• Application was amended to include the FF specification, which also includes testing and acceptance criteria for the FF PSD • Application was amended to include more detail and supportive data re: the (b) (4)

[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" was used throughout)

						(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 ○ Amorphous content of actives ○ Hygroscopicity of actives (b) (4)	4	3	4	48	(b) (4	(b) (4)		• Application was amended to include the FF specification, which also includes testing and acceptance criteria for the FF PSD • Application was amended to include more detail and supportive data re: the (b) (4) (b) (4) (b) (4) • Application is amendment to include APSD acceptance criteria requirements for individual units • Only (b) (4) form was identified for BD and GPBr, thus no

								tests for (b) (4) form are necessary • (b) (4) form control for FF is assured by the suppliers release specification
Moisture content	• moisture content of APIs and excipients, CCS components • Failure of protective packaging	2	3	3	18	(b) (4)		
Total can assay (apparent conc.)	• Incorrect formulation of one or more APIs • (b) (4) • suspension inhomogeneity	2	3	2	12			

						(b) (4)	
Degradants or impurities	• elemental impurities from synthesis, environment, or CCS components • moisture content contributes to FF degradation (most labile API)	3	3	2	18		
Leachables	• leaching from (b) (4) • leaching from (b) (4)	2	3	4	24		
Net fill weight	• incorrect fill • insufficient overfill	2	3	2	12		
Leak rate	• crimp dimension variability	2	3	2	12		

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Foreign particulate matter	• foreign particles from CCS components • foreign particles from formulation components • foreign particles from packaging used to stored components	3	3	3	27	(b) (4)	• AstraZeneca site (FEI 3003063819) responsible for drug product manufacturing is considered to be medium to low risk and has been accepted based on profile, with consideration of the site's manufacturing experience with the approved Bevespi Aerosphere of NDA 208294 and the overall compliance history

Craig Bertha

Digitally signed by Craig Bertha
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