CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214070Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) 214070
Integrated Quality Assessment Template

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RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214070
Assessment #1

Drug Product Name	Albuterol Sulfate and Budesonide Inhalation Aerosol
Dosage Form	Aerosol, metered
Proposed Strengths	108 mcg AS (equivalent to 90 mcg albuterol base) and 80 or 40 mcg BD
Route of Administration	Respiratory (Inhalation)
Rx/OTC Dispensed	Rx
Applicant	Bond Avillion 2 Development LP
US agent, if applicable	Cardinal Health Regulatory Sciences

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (SD 1)	3/10/2022	All
Quality Amendment (SD 3)	4/14/2022	Drug Product and Environmental Assessment
Quality Amendment (SD 5)	5/3/2022	Drug Product
Quality Amendment (SD 6)	5/11/2022	Drug Substance and Manufacturing
Quality Amendment (SD 9)	6/3/2022	Manufacturing
Quality Amendment (SD 10)	6/14/2022	Drug Product
Quality Amendment (SD 13)	8/5/2022	Drug Substance, Manufacturing, and Microbiology
Quality Amendment (SD 15)	8/24/2022	Manufacturing
Quality Amendment (SD 19)	11/14/2022	Manufacturing
Quality Amendment (SD 20)	11/22/2022	Manufacturing and Microbiology

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	10-JUN-2019	
	Type II			Adequate	25-JUL-2019	
	Type II			Adequate	20-MAY-2022	
	Type III			Adequate	09-APR-2015	(b) (4)
	Type IV			Adequate	06-JAN-2016	Same as for (b) (4) and (b) (4)
	Type IV			Adequate	17-FEB-2012	Same as for (b) (4) and (b) (4)
	Type III			Adequate	25-MAR-2009	Same as for (b) (4) and (b) (4)
	Type III			Adequate	19-NOV-2011	Same as for (b) (4) and (b) (4)
	Type III			Adequate	06-JAN-2016	Same as for (b) (4) and (b) (4)
	Type III			Adequate	19-APR-2012	Same as for (b) (4) and (b) (4)
	Type III			Adequate	N/A	Same as for (b) (4) and (b) (4); refer to DMF (b) (4) review
	Type III			Adequate	N/A	Same as for (b) (4) and (b) (4); refer to DMF (b) (4) review
	Type III			Not reviewed		Sufficient information provided in application
	Type III			Adequate	24-OCT-2012	
	Type III			Adequate	13-OCT-2006	
	Type III			Not reviewed		Sufficient information provided in the application.

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	141151	IND for BDA MDI from Bond Avillion (previously

		the BDA MDI was under AstraZeneca's IND [redacted] (b) (4))
NDA	208294 (Bevespi Aerosphere Inhalation Aerosol)	Cross-reference to pertinent CMC information
NDA	212122 (Breztri Aerosphere Inhalation Aerosol)	Cross-reference to pertinent information

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other				

NDA Executive Summary

1. Application/Product Information

NDA Number.	214070
Applicant Name	Bond Avillion 2 Development LP
Drug Product Name	Albuterol sulfate (AS) and budesonide (BD) inhalation aerosol
Dosage Form.	Aerosol, metered
Proposed Strength(s)	108 mcg AS (equivalent to 90 mcg albuterol base) and 80 or 40 mcg BD
Route of Administration	Respiratory (Inhalation)
Maximum Daily Dose	1.296 mg for AS and 0.96 or 0.48 mg of BD
Rx/OTC Dispensed	Rx
Proposed Indication	The albuterol sulfate (AS)/budesonide (BD) inhalation aerosol is a combination of albuterol, a beta2-adrenergic agonist and budesonide, (b) (4), indicated for the as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older.
Drug Product Description	The double fixed-combination (21 CFR 300.50) and combination product [21 CFR 3.2(e)] from Bond Avillion 2 Development LP is an inhalation aerosol that is formulated as a suspension of BD and AS with proprietary porous particles (b) (4), and with HFA-134a propellant. There are two sources of unmicronized budesonide with 3 manufacturing sites and there is one source of AS. The product is indicated for as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older. The drug product includes an integrated dose count indicator (as used for approved N (b) (4)) and it is noted that the same excipients, manufacturer, manufacturing process, canister, and valve are used for N (b) (4) as for the approved (b) (4) and (b) (4)

	[redacted](b) (4) The actuator is as for N[redacted](b) (4) but is slightly longer to accommodate a taller canister. The drugs are not NMEs and are not considered to be narrow-therapeutic. Important product characterization studies are included in attachment 2 of P.2. A report on devices returned from the clinical studies is included in attachment 4 of P.2. Based on the similarity of this product to the products of N212122 and N208294, the risks to achieving the product CQAs are fewer when compared to a product developed *de novo.*
Co-packaged product information	N/A
Device information:	The device constituent part of the combination product consists of an [redacted](b) (4) aluminum [redacted](b) (4) canister [redacted](b) (4) with a metering valve which is inserted into an actuator. The device constituent part also includes a dose indicator.
Storage Temperature/ Conditions	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]. Keep in a dry place away from heat and sunlight.

Review Team

Discipline	**Primary**	**Secondary**
Drug Substance	Sam (Sukhamaya) Bain	Lawrence Perez
Drug Product/ Labeling	Craig M. Bertha	Hong Cai
Manufacturing	Miral Patel	Ramesh Dandu & Chengjiu Hu
Biopharmaceutics	N/A	
Microbiology	Marijke Koppenol-Raab	Jesse Wells
Other (specify):		
RBPM	Anika Lalmansingh	
ATL	Craig M. Bertha	

Consults	N/A

2. Final Overall Recommendation - Adequate.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

There are no remaining deficiencies or pending issues, with the exception of editorial labeling revisions.[1]

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Pending**[1]
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

N/A

[1] The labeling review decision is pending for this IQA due to ongoing negotiations with the applicant. There are only minor labeling deficiencies from the CMC perspective and we expect the applicant will accept our recommendations. Refer to the CMC sections of the final approved labeling.

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	No, but one is planned for inclusion	Not required for approval
Established name(s)	Yes	
Route(s) of administration	Yes	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	No	See deficiency
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	

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)	Yes	This section provides priming and repriming information, as is appropriate for inhalation aerosol products

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)	Yes	
Strength(s) in metric system	No	See below
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	No	The strength uses the metric system. Albuterol sulfate is an exception as there is a monograph in the USP for an Ipratropium bromide and albuterol sulfate inhalation solution; the package insert (PI) does include the equivalency statement for the amount of albuterol base for the amount of albuterol sulfate. However, the salt policy is applied incorrectly and inconsistently (see deficiency below). In addition, the strength is given "(b) (4)" in this section and on the product labels, which is atypical.[1]
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	No	This section identifies both the strengths as well as the counts for each, consistent with labeling for approved inhalation aerosols. There is no description of the device components (see deficiency).
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

[1] Strength is typically indicated as the mass of drug delivered per actuation for MDIs. (b) (4)

The draft guidance entitled *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products – Quality Considerations* (2018) recommends that the container label include the amount of drug delivered per actuation from the mouthpiece, provides no guidance for section 3 of the package insert (PI), and is currently under revision. Thus, it may be necessary for the applicant to revise the strength in section 3 of the PI and on the labels in the future (b) (4) .

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	No, but one is planned for inclusion	No proprietary name is included, but it is not required
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	No	The salt policy is not applied correctly or consistently in the labeling (see deficiency).
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
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)	N/A	
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Yes	Color, solubility information, and octanol/water partition coefficient information provided

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 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)	Yes	
Strength(s) in metric system	No	Strengths are not provided in accordance with Agency salt policy (for albuterol sulfate).
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	
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.)	Yes	
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."	No	It is not clear that the desiccant includes a statement such as "Do not eat." See deficiency below.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	
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."	N/A	
Include information about child-resistant packaging	N/A	Section does state: "Keep out of reach of children."

1.2.5 Other Sections of Labeling

N/A

1.2.6 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	The package insert lists the following: Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850 Manufactured by: AstraZeneca Dunkerque Production (AZDP) Dunkerque, France	The PI complies with 21 CFR 201.1, as the manufacturer is listed, but it is noted that the labeling states that the product is manufactured for AstraZeneca when the applicant listed on form 356h is Bond Avillion 2 Development LP.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

In general, the patient instructions for use appear to be adequate. However, the patient instructions indicate that the "Use By Date" should be written on the actuator label in ink by the patient. The in-use period of 12 months has been established. The instructions also indicate that the inhaler should be discarded when 12 months has passed since the foil overwrap was removed (the in-use period), however, it also states that the unit should be discarded (b) (4) (b) (4) (as well as when the dose indicator reaches zero). The proposed and accepted expiration dating period or shelf life is 24 months, thus, if a pharmacy were to dispense the product after 12 months, the patient would need to discard the product when it reached the expiry, which could theoretically be before the in-use period had elapsed. DMEPA will be asked if this scenario is likely and if any additional information needs to be included in the patient instructions. If likely, instead of just instructing patients to calculate and record the in-use date, they might need to list the expiry date instead.

The current labels do not follow the USP salt policy in that the strength of albuterol sulfate is given in terms of the free base, not the salt. For comparison, the portion of the carton labels for Ventolin HFA and Proventil HFA are reproduced below:

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Proventil HFA and Ventolin HFA have “albuterol sulfate” as part of the established names. Proventil HFA provides the strength in terms of the albuterol sulfate (108 mcg) and the albuterol base (90 mcg). The Ventolin HFA label provides the same information with regard to the drug delivered from the mouthpiece, but has “90 mcg per actuation” more prominently listed as the strength under the established name (albuterol sulfate inhalation aerosol).

3.0 CARTON AND CONTAINER LABELING

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes	
Dosage strength	No	Revision needed with respect to salt policy for albuterol sulfate (see deficiency below)
Route of administration	Yes	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Yes	
Net contents (e.g. tablet count)	Yes	
"Rx only" displayed on the principal display	Yes	
NDC number	Yes	
Lot number and expiration date	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	Use By Date is recorded on the actuator back label by the user
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	Yes	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	
Medication Guide (if applicable)	No	Defer to the clinical team and DMEPA regarding the need for a medication guide
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	N/A	

Assessment of Carton and Container Labeling: Inadequate. See deficiencies below.

ITEMS FOR ADDITIONAL ASSESSMENT

Labeling Deficiencies:

1. Revise the DOSAGE FORMS AND STRENGTHS section of package insert to include a description of the product (e.g., components of the device and their appearance).

2. Revise the DESCRIPTION section of the package insert such that it complies with the recommendations put forth in the Agency guidance entitled *Naming of Drug Products Containing Salt Drug Substances* (2015; available at https://www.fda.gov/media/87247/download), i.e., with albuterol sulfate as part of the name (as an exception for historical reasons), the strength should be given in terms of the salt and the equivalency statement for the free base

should be within the parentheses).

3. Revise the HOW SUPPLIED/STORAGE AND HANDLING section of the package insert to provide the product strength in terms of the albuterol salt (i.e., 108 mcg/act).

4. Revise the DOSAGE AND ADMINISTRATION (HIGHLIGHTS section only) of the package insert, the carton, pouch, and canister labels to give the strength in terms of the emitted amount of albuterol sulfate salt, not albuterol base, and include the equivalency statements in parentheses for albuterol base (not necessary for canister label).

5. Revise the DESCRIPTION section of the package insert to include a statement that the canister should be discarded when the labeled number of actuations have been used.

6. As the product can be used as needed, revise the HOW SUPPLIED section to include the in-use periods once the foil overwrap is removed.

7. Provide confirmation that the enclosed desiccant sachets will be labeled to inform patients to not eat those items or their contents (e.g., Do not eat).

Therefore, this application is not deemed ready for approval in its present form per 21 CFR 314.125(b)(8) from ONDP perspective. However, the labeling negotiations in collaboration with DPACC and DMEPA have not completed at the time of this review.

Overall Assessment and Recommendation:

Primary Labeling Assessor Name and Date: Craig M. Bertha; 11/8/2022
Secondary Assessor Name and Date (and Secondary Summary, as needed):

Hong Cai, Division Director and Acting Branch Chief

Craig Bertha

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Hong Cai

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214070
Assessment Cycle Number	MR01
Drug Product Name/ Strength	AIRSUPRA Albuterol sulfate and budesonide inhalation aerosol 90mcg/40mcg (b) (4) and 90mcg/80mcg (28 & 120 inhalations)
Route of Administration	Inhalation via metered dose inhaler
Applicant Name	Bond Avillion 2 Development LP
Therapeutic Classification/ OND Division	OND/DPACC/OII
Manufacturing Site	AstraZeneca Dunkerque Production 224 Avenue de la Dordogne Dunkerque, Hauts-de-France 59640 France FEI: 3003063819
Method of Sterilization	Non-sterile inhalation suspension

Assessment Recommendation: **Adequate**

Assessment Summary: The proposed drug product is a fixed-dose combination product containing budesonide (BD) and albuterol sulfate (AS) in a non-aqueous suspension for inhalation. The suspension is pressure filled into a (b) (4) aluminum can (b) (4) with a metering valve.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001 Original Submission	10 March 2022
0010 Quality IR Response	14 June 2022
0013 Quality IR Response	5 August 2022
0020 Quality IR Response	22 November 2022

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: N/A

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents: N/A

S DRUG SUBSTANCE

The drug product is non-sterile. The drug substances will not be reviewed here.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(eCTD 0001 Section 3.2.P.1 Description and Composition of the Drug Product files)

Description of drug product – The drug product is a white suspension formulation in a metered dose inhaler supplied in two strengths (80/90 and 40/90 [80 or 40 µg micronized budesonide and 90 µg micronized and (b) (4) albuterol sulfate]). The drug substances are cosuspended with a porous particle excipient in a hydrofluoroalkane (HFA) propellant. (b) (4) . The DP is packaged in an aluminum can (b) (4) with a metering valve. The inhaler is wrapped in a foil (b) (4) pouch containing desiccant to provide protection from moisture (b) (4).

Drug product composition –

Ingredient	Function	Manufacturing concentration (%w/w)	
		80µg BSA/90µg AS	40µg BSA/90µg AS
Budesonide, micronized	Active Ingredient	(b) (4)	
Albuterol Sulfate, micronized (b) (4)	Active Ingredient		
Porous particles	Cosuspending agent		
HFA-134a	Propellant		

Description of container closure system –

Component	Description	Manufacturer
Can	Aluminum (b) (4) can with (b) (4)	(b) (4)
Valve	(b) (4)	
Actuator	(b) (4) mouth, body, & cap	

Assessment: *Adequate*

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain microbial control of the product.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Microbial Challenge Study

(eCTD 0001 Section 3.2.P.2 pharmaceutical-development-microbiological.pdf)

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Jesse Wells

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