

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205636Orig1s000

CHEMISTRY REVIEW(S)

NDA 205636

ProAir RespiClick (Albuterol Inhalation Powder)

Teva Branded Pharmaceutical Products R&D, Inc.

Yong Hu, Ph.D.

**Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment**

For

Division of Pulmonary, Allergy, and Rheumatology Products

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Chemistry Review Data Sheet

1. NDA: 205636
2. REVIEW #: 1
3. REVIEW DATE: 1/22/2015
4. REVIEWER: Yong Hu, Ph.D.
5. PREVIOUS DOCUMENTS:

N/A

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Response to information request	1/20/2015
Amendment (Labeling)	11/19/2014
Amendments	8/29/2014
Response to information request	8/8/2014
Amendment (Labeling)	7/28/2014
Response to information request	6/12/2014
Response to Information Request	5/23/2014
Original NDA	5/5/2014

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Branded Pharmaceutical Products R&D, Inc.

Address: 74 NW 176th Street, Miami, FL 33169

Representative: William Kiddell

Telephone: 305-575-6284

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

- a) Proprietary Name: Proair RespiClick
b) Non-Proprietary Name (USAN): Albuterol sulfate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505 (b)(2);

10. PHARMACOL. CATEGORY:

Beta2-adrenergic agonist

11. DOSAGE FORM:

Inhalation powder (Dry powder inhaler)

12. STRENGTH/POTENCY:

97 µg (metered dose); 90 µg (delivered dose)

13. ROUTE OF ADMINISTRATION:

Oral inhalation

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Bis[(1RS)-2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3
(hydroxymethyl)phenyl]ethanol]sulphate

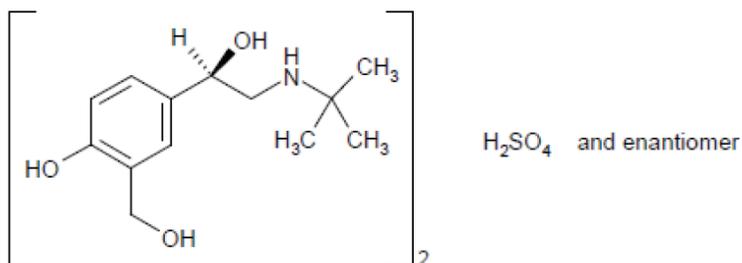
or

1,3-benzenedimethanol, alpha1-[[1,1-dimethylethyl)amino]methyl]-4-hydroxy-, sulfate (2:1)
salt

or

alpha1-[(tert-Butylamino)methyl]-4-hydroxy-m-xylene-alpha, alpha1 –diol sulfate (2:1) salt

Chemistry Review Data Sheet



Molecular Formula: $(\text{C}_{13}\text{H}_{21}\text{NO}_3)_2 \cdot \text{H}_2\text{SO}_4$

Molecular weight: 576.7

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	12/29/2014	
	III			4	N/A		
	IV			4	N/A		
	IV			4	N/A		
	IV			4	N/A		

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")

Chemistry Review Data Sheet

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	104532	This was the IND supporting the NDA.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not requested.		
EES	Pending.		
Pharm/Tox	The impurity specifications are acceptable.		Email communications with the reviewer Dr. Nikunj Patel
Biopharm	Not requested.		
LNC	Not requested.		
Methods Validation	Not requested. Commonly-used analytical methods for this type of product.		
OPDRA	Not requested.		
EA	Categorical exclusion	See this review	Dr. Yong Hu
Microbiology	Not requested.		

The Chemistry Review for NDA 202450

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for approval pending the Office of Compliance's "Acceptable" recommendation for the manufacturing and testing facilities.

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

N/A.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is (b) (4) albuterol sulfate, manufactured by (b) (4) under DMF (b) (4) and (b) (4). It is the same drug substance sourced for the approved product ProAir HFA (albuterol MDI) marketed by the same applicant. The drug substance specification is (b) (4)

(b) (4) Particle size distribution, amorphous content, identification, assay, related substances, heavy metals, residual solvents, water content, and microbial limits are among the critical attributes to be controlled in the drug substance specification.

The product is a device-metered, inspiratory-flow driven, multi-dose dry powder inhaler (so-called Albuterol MDPI). The inhalation powder product contains a formulation mixture of albuterol sulfate and lactose monohydrate in its reservoir (hopper). The device meters 97 µg and delivers 90 µg of albuterol free base from the inhaler mouthpiece at each actuation. The product contains a minimum of 200 doses and has an integrated dose counter which displays the number of doses remaining. The inhaler is over-wrapped with a heat sealed aluminum foil pouch.

The device operates in three distinct steps: open the mouthpiece cover to meter a specific dose of medicine, inhale the dose, and close the mouthpiece cover to re-set the device ready for the next dose. This dry powder inhaler (DPI) product is intended to overcome the difficulty in patient's coordinating the "press and breathe" steps in the use of the albuterol MDIs (such as ProAir HFA). This DPI product was developed to match the in-vivo performance of the ProAir HFA, 90 µg.

Executive Summary Section

The device evolved from the (b) (4) variant to the (b) (4) variant (to-be-marketed) after the first pivotal clinical trial ABS-AS-306 and the manufacture of the first three registration stability batches. All subsequent clinical trials and stability batches were manufactured using the to-be-marketed (b) (4) device. The improvements seem to be minor changes, which did not impact dose metering and dose delivery.

The device components and sub-assemblies are manufactured by (b) (4) and the final drug product by Teve Pharmaceutical Industries, Ltd., Israel. All pivotal clinical trial supplies and registration stability batches were manufactured using the final to-be-marketed powder formulation at the proposed commercial scale (b) (4). The drug product manufacturing process involves (b) (4)

(b) (4)

(b) (4)

The applicant presented two Comparability Protocols in the Pharmaceutical Development section. They are to support an (b) (4) material (b) (4) of the device and a second manufacturing site for the device components. Both protocols are deemed acceptable for future CBE-30 supplements.

The critical quality attributes of the drug product include delivered dose uniformity (DDU), aerodynamic particle size distribution (APSD), related substances, assay (total drug content per inhaler), identification, microbial limits, dose counter reading, and foreign particulates. All these attributes are controlled in the product specification. The critical material attributes for the sole excipient, lactose monohydrate, include particle size and amorphous content. Amorphous content in the lactose has been shown to be undetectable (limit of detection: (b) (4)%) in all batches used so far, thus will not be routinely analyzed.

The drug product stability program consists of the following nine batches:

- Three stability batches using the (b) (4) device variant and (b) (4) one of which was used in the Phase 3 clinical program. 36 months long-term stability data were provided.
- Three additional stability batches using the (b) (4) device variant (commercial device) and (b) (4) one of which was used in the Phase 3 clinical program. 12 months long-term stability data were provided.

Executive Summary Section

- Three additional stability batches using (b) (4) device variant and (b) (4) Six months long-term stability data were provided.

Teva proposes a (b) (4) month expiration dating period for the drug product, with the inhaler stored within its protect packaging, either in the upright or inverted orientation. The proposal is based on an analysis of real time accelerated stability data generated at 6 months and controlled room temperature stability data generated at 36 months for (b) (4) drug product batches. However, since the available real-time 12-month data for the (b) (4) batches only predict 24 months shelf life so far, with the supporting 36 months data for the (b) (4) batches, this reviewer recommends an expiration dating period of 36 months for the NDA approval.

B. Description of How the Drug Product is Intended to be Used

The product is for oral inhalation only.

The inhaler is operated by the patient as follows: The patient holds the device in an upright position. The patient opens the mouthpiece cover fully, exhales, places the mouthpiece between the lips, inhales forcefully and deeply, and removes the inhaler from his/her mouth. The patient then holds his/her breath for ten seconds, or as long as comfortably possible. The patient finally breathes out slowly and then closes the mouthpiece cover.

The inhaler does not require priming and routine cleaning. The inhaler should not be used with a spacer.

The product should be stored under controlled room temperature within protective foil packaging. Once the foil packaging has been removed, the product should be used within 13 months when stored at controlled room temperature .

C. Basis for Approvability or Not-Approval Recommendation

The NDA has provided adequate information to assure the identify, purity, strength, and quality of the proposed product.

The risk mitigation is acceptable as shown in the table below.

Executive Summary Section

Initial Quality Assessment			Current Review Assessment		
CQAs	Factors affecting CQAs	Risk ranking	Risk mitigation approach	Risk evaluation	Life-cycle considerations/comments
Delivered dose uniformity (DDU)	Inhomogeneity or low formulation assay of albuterol sulfate/lactose blend (e.g., from manufacturing; result of shipping); Lower than target fill of reservoir; Failure of protective packaging (moisture ingress); Amorphous content of API; Device malfunction; Particle size/amorphous content of lactose; Static charge of formulation	8	<p>Particle size of lactose is controlled in the specification. Amorphous content of lactose is undetectable (below (b) (4) %). The amorphous content of API is controlled in the API specification to be below (b) (4) %. The blend uniformity is assured by the process parameters established using DOE studies and the in-process test (b) (4).</p> <p>The packaged inhalers are 100% checked for foil seal integrity. The DDU throughout inhaler life is tested for product release and stability. The device appears robust based on the characterization studies.</p>	Acceptable	Teve committed to revisit the acceptance criterion for the API amorphous content once data from 15 batches of drug substance is available or one year after the product is launched.
Aerodynamic particle size distribution (APSD)	Inhomogeneity or low assay of albuterol sulfate/lactose blend; Lower than target fill of reservoir; Failure of protective packaging; Particle size distribution of API; Amorphous content of API; Device malfunction; Particle size/amorphous content of lactose; Composition of device air flow path components; Device flow resistance variation; Static charge of formulation	8	<p>Particle size of lactose is controlled in the specification. Amorphous content of lactose is undetectable (below (b) (4) %). The amorphous content of API is controlled in the API specification to be below (b) (4) %. The blend uniformity is assured by the process parameters established using DOE studies and the in-process test (b) (4).</p> <p>The packaged inhalers are 100% checked for foil seal integrity. The APSD is tested for product release and stability. The device appears robust based on the characterization studies. For example, the APSD is not affected when (b) (4).</p>	Acceptable	
Purity (impurities/degradants)	Degradation of API as formulated; Input purity of API; Input purity of lactose	4	The input API and lactose have suitable specifications for impurity control. The degradants are also controlled by the product specification. The product is protected by aluminum foil and stored at controlled room temperature. Extensive stability data show that degradation is not a significant issue for this product, even when the inhalers were stored unwrapped at 30 C/65% RH for 24 months.	Acceptable	

Chemistry Assessment Section

Chemistry Assessment**I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:
Body Of Data**

S DRUG SUBSTANCE [Albuterol sulfate, (b) (4)]

Adequate.

The drug substance information is provided in DMF (b) (4), which has been deemed adequate. The following information from the NDA is reviewed.

The nomenclature of the drug substance is shown below.

INN Name

Salbutamol sulphate

Chemical Abstract Service (CAS)

51022-70-9

Chemical Name(s)

Bis[(1RS)-2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol]sulphate

or

1,3-benzenedimethanol, alpha1-[[1,1-dimethylethyl)amino]methyl]-4-hydroxy-, sulfate (2:1) salt

or

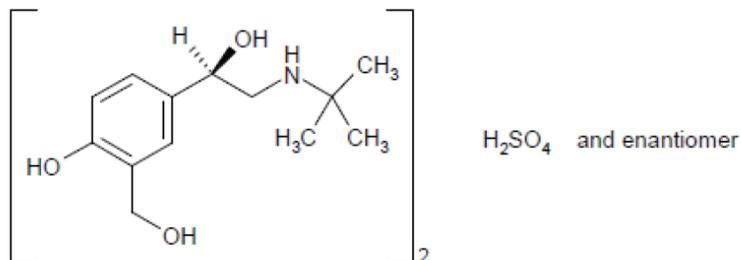
alpha1-[(tert-Butylamino)methyl]-4-hydroxy-m-xylene-alpha, alpha1 -diol sulfate (2:1) salt

USAN Name

Albuterol sulfate

The structure formula, molecular formula, molecular weight are presented below.

Chemistry Assessment Section

Structural Formula**Figure 1: Structural Formula of Albuterol Sulfate****Molecular Formula** $(\text{C}_{13}\text{H}_{21}\text{NO}_3)_2 \cdot \text{H}_2\text{SO}_4$ **Relative Molecular Weight**

576.7

Albuterol sulfate is manufactured by (b) (4) under DMF # (b) (4) and is the same drug substance as that used for the marketed ProAir HFA (albuterol sulfate) Inhalation Aerosol (NDA 21-457). (b) (4)

Table 1: Facilities for Albuterol Sulfate Manufacturing, (b) (4) and Testing

Drug Substance Manufacturer	(b) (4) Facility	Drug Substance Testing Facility
(b) (4)	(b) (4)	Teva Pharmaceutical Industries, Ltd. 20 th Kiryat HaMada Street, Har Hozvim Industrial Zone, Jerusalem 9777600 Israel

DMF (b) (4) has provided adequate manufacturing process information and process controls for albuterol sulfate (b) (4)

(b) (4)

Chemistry Assessment Section

(b) (4)



The ^{(b) (4)} drug substance specification (see below) meets the requirements in the USP monograph for albuterol sulfate . ^{(b) (4)}



Chemistry Assessment Section

Table 1: Specifications for albuterol sulfate

Test	Acceptance Criteria	Analytical Method
Characteristics		
Appearance	A white or almost white, crystalline powder.	In-house
Color of Solution	A ^{(b) (4)} solution in water is clear and not more intensely colored than ^{(b) (4)} reference solution.	European Pharmacopoeia, Chapter 2.2.2, Method II
Crystalline Form- ^{(b) (4)} Microscope	Particle Shape- Primarily ^{(b) (4)} ^{(b) (4)}	In-house/ USP <776>
Crystalline Form- Amorphous Content	NMT ^{(b) (4)} %	In-house (QDS0035452)
Identification		
Identification by Infrared	The frequency and relative intensity of the absorption peaks in the sample spectrum corresponds to those that are characteristic of the drug substance in the reference standard.	USP <197K>
Identification by UV	The ultra violet absorption spectra of the test solution and the standard solution exhibit maxima and minima at similar wavelengths.	USP <197U>
ID sulfates	Reactions, characteristic to sulfates.	USP <191>
ID by HPLC	The retention time of the major peak in the chromatogram of the assay preparation corresponds to that of the chromatogram of the standard preparation, as obtained in the assay.	Albuterol sulfate USP monograph
Water Content	Not more than 0.5%	USP <921>
Residue on Ignition	Not more than 0.1%	USP <281>
Chromatographic Purity	Any impurity: NMT ^{(b) (4)} % Total impurities: NMT ^{(b) (4)} %	Albuterol sulfate USP monograph
Assay	98.5 – 101.0%. Calculated on the anhydrous basis.	Albuterol sulfate USP monograph
Specific Optical Rotation	^{(b) (4)} calculated on the anhydrous basis.	USP <781S>

Chemistry Assessment Section

Test	Acceptance Criteria	Analytical Method
Related Substances	<div style="background-color: #cccccc; width: 100%; height: 150px; margin-bottom: 5px;"></div> Any unspecified impurities Total specified impurities Total unspecified Total impurities	NMT (b) (4) % NMT (b) (4) %
Particle Size Distribution	D ₉₀ (b) (4) micron D ₅₀ (b) (4) micron D ₁₀ (b) (4) micron Span (b) (4)	In-house (QDS0008071)
Heavy Metals	NMT (b) (4) ppm	In-house (QDS0008071)
Residual Solvents	(b) (4) NMT (b) (4) ppm ^{a)}	In-house (QDS0008071)
Microbiological Examination	Total Aerobic Microbial Count (TAMC) NMT (b) (4) cfu/g Total Combined Mould and Yeast (TYMC) NMT (b) (4) cfu/g Absence of: Staphylococcus aureus/g Confirmed Pseudomonas aeruginosa/g Confirmed Salmonella species/10g Confirmed Escherichia coli/g Confirmed Bile Tolerant Gram Negative Bacteria/g Confirmed	In-house (QDS0009414)

^{a)} Based on (b) (4) statement, no Class 1, Class 3 or other organic solvents are likely to be present.

Chemistry Assessment Section

The amorphous content of the drug substance is measured by the [REDACTED] (b) (4). The method appears suitable for the determination of amorphous content in albuterol sulfate as the results of the linear regression indicated good linear correlation suitable for quantitative analysis of amorphous content down to [REDACTED] (b) (4)%.

Table 1 below contains a list of all batch data generated on the amorphous content. The results show that the amorphous content of the albuterol batches was in the range of [REDACTED] (b) (4)%. The mean content was about [REDACTED] (b) (4)% and the standard deviation [REDACTED] (b) (4)%. The applicant proposes an acceptance criterion of Not More Than (NMT) [REDACTED] (b) (4)% and states that the acceptance criterion will be revisited once data from 15 batches of drug substance is available or one year after the product is launched on the market, whichever is sooner. This proposal is acceptable given the limited data at this stage.

Table 1: Amorphous Content results for Albuterol Sulfate Pre-validation Testing

Vendor B/N	Clinical / exhibit batches	% Amorphous content
(b) (4)		

Note: N/A as batches were sourced from ProAir® HFA inventory.

Chemistry Assessment Section

P DRUG PRODUCT [Albuterol, Inhalation Powder]
P.1 Description and Composition of the Drug Product [Albuterol, Inhalation Powder]

Adequate.

The product is a device-metered, breath-actuated, multi-dose dry powder inhaler (so-called Albuterol MDPI). The inhalation powder product contains a mixture of albuterol sulfate and lactose monohydrate, delivering 90 µg of albuterol free base from the inhaler mouthpiece at each actuation. The metered dose is 97 µg of albuterol free base. For dry powder inhalers (DPIs), the strength of the product is expressed as the metered dose, as opposed to delivered dose for metered dose inhalers (MDIs). Therefore, the strength of the product is 97 µg (albuterol base).

The product contains a minimum of 200 doses and has an integrated dose counter which displays the number of doses remaining. The inhaler is over-wrapped with a heat sealed aluminum foil pouch.

The quantitative composition of the product is shown below.

Table 1: Quantity per Container

Ingredients	Quantity	Function	Reference to standards
Albuterol sulfate	(b) (4) mg	Active substance	USP
Lactose monohydrate	(b) (4) g	(b) (4)	USP NF
<i>Target fill weight per device</i>	0.65 g		
<i>Fraction of drug substance (%w/w)</i>	(b) (4) %		

Table 2: Unit Formula

Ingredients	Ex-actuator ^a
Albuterol sulfate	108 mcg ^b
Lactose monohydrate	(b) (4)

^a Test conditions - airflow rate, Q, that produces a pressure drop of (b) (4) over the inhaler to be tested and at a duration consistent with the withdrawal of 2 L of air from the mouthpiece of the inhaler

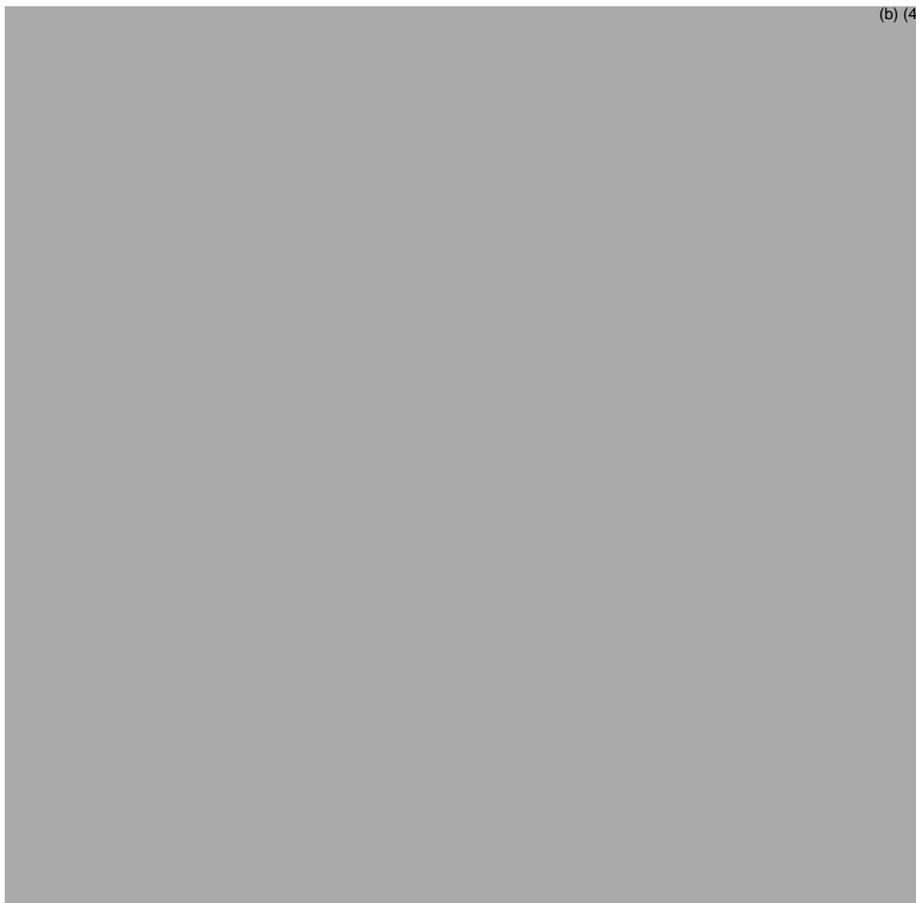
^b Equivalent to 90.0 mcg albuterol

The Albuterol MDPI device consists of an assembly of a (b) (4) and the following subassemblies: (b) (4)

Chemistry Assessment Section

The schematic showing of the sub-assemblies can be found below. Details of the device component parts are described in Section 3.2.P.7.1 Description.

Figure 1: Schematic Showing Sub-Assemblies of Albuterol MDPI Inhaler



The inhaler is operated by the patient as follows: The patient holds the device in an upright position. The patient opens the mouthpiece cover fully, exhales, places the mouthpiece between the lips, inhales forcefully and deeply, and removes the inhaler from his/her mouth. The patient then holds his/her breath for ten seconds, or as long as comfortably possible. The patient finally breathes out slowly and then closes the mouthpiece cover.

P.2 Pharmaceutical Development [Albuterol, Inhalation Powder]
P.2.1 Components of the Drug Product

The product is comprised of a hard plastic case, within which a reservoir (or hopper) contains a drug powder formulation consisting of albuterol sulfate drug substance and lactose monohydrate as the only excipient. The device has an internal mechanism governing the metering of individual doses, a mouthpiece through which the dose is inhaled, and an attached mouthpiece

Chemistry Assessment Section

cover. The product contains a minimum of 200 doses and has an integrated dose counter which displays the number of doses remaining. The inhaler is over-wrapped with a heat sealed aluminum foil pouch.

P.2.1.1 Drug Substance

Particle size:

The representative particle size distribution (PSD) data for the drug substance prior to (b) (4) is shown below.

Table 1: Particle Size Distribution of (b) (4) Albuterol Sulfate

Critical Material Attribute	Specification	811720	850104	731720*
Particle size (microns)	(b) (4)			
(b) (4) lot No.	N/A	124A0030	124A0032	104A0012

*731720 was released to the previous spec of (b) (4)

The particle size distribution of (b) (4) albuterol sulfate is a critical material attribute (CMA) in determining the aerodynamic particle size of the final drug product. The development of the particle size of the (b) (4) drug substance (b) (4) for the Albuterol MDPI program. Different lots of (b) (4) albuterol sulfate batches were employed in the development of Albuterol MDPI as reflected in Table 2 below. The PSD method was based on (b) (4)

Table 2: Particle Size Distribution of (b) (4) Drug Substance Batches Employed in the Development of Albuterol MDPI

Teva batch number	Finished product campaign	Particle Size Distribution			
		D10 microns	D50 microns	D90 microns	Span
1021811	Phase 1/2	(b) (4)			
104A0012	Phase 3 clinical/exhibit	(b) (4)			
104A0013	Phase 3 exhibit	(b) (4)			
104A0014	Phase 3 exhibit	(b) (4)			
124A0003	Phase 3 clinical/exhibit	(b) (4)			
124A0030	Phase 3 exhibit	(b) (4)			
124A0032	Phase 3 clinical/exhibit	(b) (4)			

Chemistry Assessment Section

(b) (4)

P.2.2 Drug Product

There are three albuterol sulfate press-and-breathe metered dose inhaler (MDI) products (ProAir® HFA, Proventil HFA and Ventolin HFA) marketed in the United States. The applicant states that it is well known that many asthma patients do not use their MDIs correctly and find difficulty in coordinating the “press and breathe” instruction. The applicant has thus intended to develop a proprietary Multi-dose Dry Powder Inhaler (MDPI) to overcome these co-ordination issues; the patient’s own inspiratory effort is directly linked to the delivery of a dose of medication.

Albuterol MDPI product also intends to remove the need for inhaler priming before use and requires no periodic cleaning to prevent blocking, as is the case with the marketed MDI products.

Teva’s MDPI is designed to fit within the palm of a patient’s hand and have a minimum number of operating steps (open the mouthpiece cover to meter the dose; inhale the dose; close the mouthpiece cover to reset the device).

Albuterol MDPI was developed (b) (4) performance of ProAir® HFA (albuterol sulfate inhalation aerosol, 90 mcg) marketed in the United States (NDA-21-457) by the applicant.

P.2.2.1 Formulation Development

All the pivotal clinical and stability batches are summarized in Table 29. The final to-be-marketed formulation ((b) (4)% w/w blend) was used in all batches for pivotal clinical trials and stability study. The batches were manufactured at the commercial scale (b) (4)

Chemistry Assessment Section

Table 29: Summary of Pilot and Pivotal Clinical/Stability Batches Investigated as Part of the Albuterol MDPI Development Program

Campaign	Batch number	Purpose	Date of manufacture	Blend concentration % w/w	Scale	Device	Filling machine supplier
Phase 1/2	RD0902	ABS-AS-101 ABS-AS-201	2009	(b) (4)			
First Pivotal	MD2001	ABS-AS-306	2010				
	MD2003	Exhibit	2010				
	MD2004	Exhibit	2010				
Second Pivotal	AB1001	ABS-AS-301, ABS-AS-302, ABS-AS-304, ABS-AS-307	2012				
	AB1002	Exhibit	2012				
	AB1004	Exhibit	2012				
	AB3001	ABS-AS-308	2013				
Third Pivotal	AB4001	Exhibit	2013				
	AB4002	Exhibit	2013				
	AB4003	Exhibit	2013				

Some notable changes occurred during the timeframe in which clinical and stability batches were manufactured: a change in device iteration (b) (4) as highlighted in Section 3.2.P.2.4 and additional supplier of (b) (4) was introduced as outlined in Section 3.2.P.2.3. The device variant was updated from (b) (4) to (b) (4) in order to address potential device failure from mis-use (repeatedly opening and closing the mouthpiece cover without taking a dose) and observations made during pre-verification testing. The final commercial product will be manufactured using (b) (4)

P.2.2.2 Overages

Albuterol MDPI was developed to ensure each individual inhaler contains a minimum quantity of powder blend to ensure delivery beyond the nominal label claim of 200 doses (even when the device is used off the vertical orientation). The fill weight of powder blend target per inhaler and the proposed range for the commercial filling process is outlined in Table 30.

Chemistry Assessment Section

Table 30: Albuterol MDPI Fill Weight Target per Inhaler and Proposed Range for Commercial Manufacturing

(b) (4)

**P.2.2.3 *Physicochemical and Biological Properties***

One of the most critical properties of the product is aerodynamic particle size distribution (APSD). Figure 10 compares the APSD profiles of pivotal clinical/stability drug product batches and it is clear that the profiles are comparable.

Chemistry Assessment Section

Figure 10: Comparison of the APSD Profiles of Batch RD0902 (Phase 1 & 2) to Phase 3 Exhibit Batches



P.2.3 Manufacturing Process Development

The development of the manufacturing process encompassing [REDACTED] is described in Figure 1.

(b) (4)

4 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Chemistry Assessment Section

(b) (4)

P.2.4 Container Closure System

The Albuterol MDPI product is a reservoir type, inspiratory flow driven, multi-dose dry powder inhaler. The design is based on [REDACTED] (b) (4) and operates in three distinct steps: open the mouthpiece cover to meter a specific dose of medicine, inhale the dose, and close the mouthpiece cover to re-set the device ready for the next dose. A dose counter decrements each time a dose is taken.

The inhaler consists of [REDACTED] (b) (4)

These sub-assemblies combine to enable the Albuterol MDPI device to operate as follows:

- As the patient opens the mouthpiece cover, the device dispenses a metered dose of the drug [REDACTED] (b) (4) and then transfers this metered dose to the inhalation position.
- The patient inhales through the mouthpiece and receives the metered dose of medicine.
- As the patient closes the mouthpiece cover, the metering mechanism is reset and the counter mechanism decrements by one count.

The materials selected for drug-product contact and user contact components of the device are [REDACTED] (b) (4). The secondary packaging used is a heat-sealed aluminum foil laminate.

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Chemistry Assessment Section

Evaluation of Clinical Trial Complaint Samples and Due Diligence Samples from Phase 3 Clinical Trials ABS-AS-301, ABS-AS-302, ABS-AS-304, ABSAS- 307 and ABS-AS-308 for Albuterol MDPI

There were 5652 devices in total used across the five Phase 3 clinical studies for Albuterol MDPI. A total of twenty-seven complaint samples and seven due diligence samples were thoroughly investigated from these clinical studies. The thirty four devices that were investigated accounted for 0.6% of the total number of devices used by patients across the five Phase 3 clinical studies for Albuterol MDPI:

- Eight clinical complaint samples were reported to contain broken/dislocated mouthpiece covers.
- Nine clinical samples were reported that the patient did not feel delivery of medication.
- Four clinical samples were reported to cause patient discomfort (plastic component touching the lips of the patient when inhaling a dose).
- One clinical sample was reported that the dose counter mechanism was not working as intended.
- Seven due diligence samples were identified for investigation from the ABS-AS-308 study; one device was identified during the conduct of the study and six devices were identified after data analysis. The data showed that the dose counter readings in these devices were outliers compared to patient diary entries.
- Five clinical samples were reported that the device did not work after being submerged in water.

The investigation results are summarized below.

Chemistry Assessment Section

Table 4: Summary of the Investigational Results for Each Complaint Category

Investigation Result	Complaint Type					
	Broken / Dislocated Mouthpiece Cover	Medication not Delivered / Dose Perception	Patient Discomfort	Counter Mechanism not Working	Due Diligence	Other
Patient Misuse / Handling of Device	3	0	0	0	0	0
Device Subjected to Conditions Beyond Normal Use	2	0	0	0	0	5
Device Subjected to High Impact Damage	1	0	0	0	0	0
Patient Device Operational Fault	1	4	0	0	0	0
Device Functioning as Intended – Dose Delivery Perception	0	5	0	0	0	0
Device Functioning as Intended	1	0	4	1	7	0
Total	8	9	4	1	7	5

The complaint devices functioned as intended; where exceptions applied, the device was misused, subject to conditions beyond normal use, or not operated as instructed.

Container closure system – extractables and leachables

Dry Powder Inhalers (DPIs) in general pose a lower risk for leachables than typical Metered Dose Inhalers (FDA May, 1999 - Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics) where solvents facilitate leaching from the container closure system. Albuterol MDPI Inhalation Powder product contains a dry powder formulation and correspondingly has a low potential for container closure interaction. In addition, ^{(b) (4)} are used in the devices, further supporting the low risk for leachables.

Whilst packaging interaction is likely to be low, the applicant assessed the critical components, i.e. those in contact with the formulation or patient’s mucosa, for extractables. The applicant also carried out a leachables study for three batches of product in upright and inverted orientations under 25 °C/60% RH and 40 °C/75% RH. Recommendations proposed by the Product Quality Research Institute (PQRI) document – Safety Thresholds and Best Practices for Extractables and

Chemistry Assessment Section

Leachables in Orally Inhaled and Nasal Drug Products (8 September 2006) were followed in the studies.

No extractable or leachable compound has been identified at a level that would pose a risk to the patient.

Container Closure System Manufacturing

(b) (4)

Chemistry Assessment Section

(b) (4)

P.2.5 Microbiological Attributes

The dry powder drug substance is expected to have a [REDACTED] ^{(b) (4)} and on this basis it does not present a matrix congruent for microbial proliferation. Nonetheless, the drug substance is tested for estimation of the number of viable aerobic microorganisms present and for absence of designated microbial species. The excipient lactose monohydrate is also tested according to these criteria. The device components are manufactured under GMP conditions in clean room environments. The microbial specification is in place for the drug product.

Examination of stability samples for Albuterol MDPI pivotal and exhibit batches stored for up to 36 months demonstrated the absence of detectable levels of microorganisms. No microbial growth was detected when returned clinical inhalers from the long term safety study ABS-AS-307 were tested.

Chemistry Assessment Section

P.3 Manufacture [Albuterol, Inhalation Powder]**P.3.1 *Manufacturers*****Evaluation: Pending.**

The name and address of the manufacturer responsible for manufacture, packaging, release and stability testing of commercial product is:

Teva Pharmaceutical Industries, Ltd.
2 Hamarpe Street
Jerusalem 9777402
Israel
FEI: 3003414719
DUNS: 533065822

Release and stability examination for foreign particulate testing will be conducted at (b) (4) or at Teva Pharmaceutical Industries, Ltd. (2 Hamarpe Street, Jerusalem).

(b) (4)

Manufacturer of device parts (Listed on Form 356h):

(b) (4)

Extractables and Leachables testing (Listed on Form 356h):

(b) (4)

P.3.2 *Batch Formula***Adequate.**

Table 1 below outlines the quantities of active ingredient and excipient per (b) (4) batch ((b) (4) inhalers), which is the planned commercial batch size. The batch formula is consistent with the phase 3 formulation.

Chemistry Assessment Section

Table 1: Manufacturing Formula for a Batch Size of (b) (4)

Materials	Function	Supplier	Quantity per actuation	Quantity per inhaler	Quantity per batch (b) (4)
Albuterol sulfate USP (b) (4)	Active	(b) (4)	108 mcg	(b) (4)	(b) (4)
Lactose monohydrate USP/NF	Excipient	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Target fill weight per device	Not applicable	Not applicable	Not applicable	0.65 g	Not applicable

(b) (4)

P.3.3 Description of Manufacturing Process and Process Controls

Adequate.

Table 1 below lists the (b) (4) procedures for the product. The proposed manufacturing process is represented in the flow chart shown in Figure 1.

The master batch record is provided in this section. The master batch record and the process are consistent with those for the manufacture of the registration batches, thus acceptable. Note the clinical batches and stability batches were manufactured at the final commercial scale. The process development information in the Pharmaceutical Development section also supports the proposed process.

Each filled device contains a minimum of approximately (b) (4) % overage of the formulation to ensure each device always delivers the claimed number of doses.

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Chemistry Assessment Section

(b) (4)

P.3.5 Process Validation and/or Evaluation**Adequate.**

The applicant states that process validation will be performed prior to product launch. Full scale process validation of the manufacturing process will be performed on three batches of Albuterol MDPI at the commercial scale and on the manufacturing line intended for commercial manufacture.

P.4 Control of Excipients [Albuterol, Inhalation Powder]**P.4.1 Specifications [Albuterol, Inhalation Powder]****Adequate.**

The only excipient used in the product is (b) (4) (Lactose Monohydrate, NF) manufactured by (b) (4)

The excipient complies with the USP/NF monograph for lactose monohydrate. Additional tests are also performed on the excipient. The specification is shown below.

Chemistry Assessment Section

Test	Acceptance Criteria	Analytical Procedure
Description	White, (b) (4) powder	QGM000079
Solubility	(b) (4)	USP
Clarity and color of solution		NF monograph
Identification A: Infrared absorption		NF monograph
B: TLC		NF monograph
Optical rotation (specific rotation)		NF monograph

Test	Acceptance Criteria	Analytical Procedure
Microbial enumeration tests and Tests for specified microorganisms *	Total combined yeasts and molds count (TYMC) does not exceed (b) (4) cfu/g Total aerobic microbial count (TAMC) does not exceed (b) (4) cfu/g <i>Escherichia coli</i> – Absent/g	QEX0006202
Acidity or alkalinity	The solution is colorless, and NMT 0.4 mL (b) (4) (b) (4)	NF monograph
Loss on drying	The monohydrate form loses NMT 0.5% of its weight.	NF monograph
Water	4.5% - 5.5%	NF monograph
Residue on ignition	NNT 0.1%	NF monograph
Heavy metals	The limit is 5 µg/g.	NF monograph
Protein and light-absorbing impurities	The absorbance divided by the path length, in cm, is NMT 0.25 in the range of 210-220 nm and is NMT 0.07 in the range of 270-300 nm.	NF monograph

Additional tests and acceptance criteria:

PARTICLE SIZE DISTRIBUTION by the method QEX0007504:

d10 = (b) (4) µm

Chemistry Assessment Section

d50 = (b) (4) μm
d90 = (b) (4) μm
% < (b) (4) = (b) (4) %

DETERMINATION OF ANOMERIC PURITY BY GC (method QEX0007519):

(b) (4): NMT (b) (4) %

SPECIFIC AND QUANTITATIVE PROTEIN CONTENT (method QEX0007521):

Protein concentration: NMT (b) (4) ppm

DETERMINATION OF PARTICLE SHAPE AND MORPHOLOGY (method QEX0007516)

An homogenous size distribution is observed. The crystalline particles are (b) (4)

ASSAY (method QEX0007515): (b) (4) %

RELATED SUBSTANCES FOR LACTOSE MONOHYDRATE (Method QEX0011872):

NMT (b) (4) % (b) (4)

NMT (b) (4) % (b) (4)

MICROBIOLOGICAL EXAMINATION (Method QEX0006202)

Total combined yeasts/molds count (TYMC): NMT (b) (4) CFU/1 g

Total aerobic microbial count (TAMC): NMT (b) (4) CFU/1 g

Escherichia coli – Absent/g

Pseudomonas aeruginosa - Absent/g

Staphylococcus aureus - Absent/g

Bile tolerant gram negative bacteria - Absent/g

BACTERIAL ENDOTOXIN (QEX0006210):

Bacterial Endotoxins NMT (b) (4) EU/g

Amorphous content is not routinely analyzed. See justification in P4.4

P.4.2 Analytical Procedures

Adequate.

The non-compendial methods are briefly described below.

Particle size:

Measured using (b) (4) Particle size Analyzer for the dry powder.

Determination of anomeric purity:

Gas chromatograph with (b) (4), autoinjector.

Chemistry Assessment Section

Protein content:

Measured by spectrophotometer to determine the proteins' reaction with [REDACTED] (b) (4).

Particle shape and morphology:

Determined by using [REDACTED] (b) (4) microscope.

Assay and related substances:

Determined by HPLC.

Microbiological examination:

The Method complies with USP<61> and USP<62>.

Bacterial endotoxin:

The method complies with USP <85>.

P.4.3 Validation of Analytical Procedures**Adequate.**

The method for determination of particle size distribution has been validated by demonstrating method suitability, ruggedness and robustness.

The method for assay has been validated by demonstrating acceptable specificity, accuracy and precision, ruggedness, robustness and linearity.

The method for related substances has been validated by demonstrating acceptable specificity, accuracy and precision, ruggedness, robustness and limit of detection.

The method for the determination of protein has been validated by demonstrating method suitability and ruggedness.

The method for the determination of the anomeric purity has been validated by demonstrating acceptable specificity, linearity, ruggedness, accuracy and precision, limit of detection and limit of quantitation.

P.4.4 Justification of Specifications**Adequate.**

Lactose Monohydrate is a USP NF compendial excipient. The specifications for identification (Fourier Transform Infra Red Spectroscopy and Thin Layer Chromatography); water determination; clarity and color of solution; acidity and alkalinity; specific optical rotation; protein and light absorbing impurities; heavy metals; residue on ignition; and loss on drying are taken from the USP monograph.

Chemistry Assessment Section

In addition to the USP monograph, the specification includes tests for assay; particle shape and morphology; specific and quantitative protein content; morphic form; anomeric purity; impurities and degradants; endotoxins; particle size distribution; and microbial tests.

The assay acceptance criterion is justified by the release data (b) (4) of ten batches of lactose monohydrate used in the manufacturing of the clinical and registration drug product batches.

The acceptance criterion for the particle size is also justified by the data (see Table 12 below) for the ten lactose batches (also see evaluation in Pharmaceutical Development Section).

Table 12: Calculation of Revised PSD Acceptance Criteria for Lactose Monohydrate

	Particle size distribution			
	D10 (µm)	D50 (µm)	D90 (µm)	% < (b) (4) microns
Mean	(b) (4)			
Standard deviation				
Mean – 3 x SD				
Mean + 3 x SD				
Limits				

The acceptance criteria for shape, protein content, anomeric purity, endotoxin, and related substances are also justified by the batch data of the ten lactose batches.

The tests and acceptance criteria for microbial examination are consistent with the recommendations in USP <1111> and the lactose monohydrate USP monograph.

The amorphous content of 16 batches of lactose was measured by DSC method. The limit of quantification (LOQ) of this method is (b) (4)%. There was no detectable amorphous content above LOQ therefore the applicant proposes not to analyze the amorphous content as part of the routine release testing. However, should the manufacturer change the process, the first 3 batches will be tested for amorphous content (acceptance criteria NMT (b) (4)%). This proposal is reasonable.

P.4.5 Excipients of Human or Animal Origin

Adequate.

The excipient (lactose monohydrate) (b) (4). The TSE/ BSE statement for lactose monohydrate is provided. Based on OPS policy, lactose carries low risk of BSE/TSE contamination.

P.4.6 Novel Excipients

Chemistry Assessment Section

Not applicable.

P.5 Control of Drug Product [Albuterol, Inhalation Powder]
P.5.1 Specification(s)

Adequate.

The originally proposed specification is as follows.

(b) (4)



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Chemistry Assessment Section

(b) (4)

After evaluation of the product data, the CMC team sent the following comments to the applicant. The applicant provided responses via an email to the project manager, Leila Hann.

1. Revise the drug product specification as follows:

(b) (4)

Chemistry Assessment Section

(b) (4)



The applicant has provided the revised specification as follows.

Release & Shelf Life Specifications

<u>Test</u>	<u>Method</u>	<u>Use^{1,2}</u>	<u>Acceptance Criteria</u>
Description	QDP0014271	R+S	Device color: Compiles with standard
		R	Dose counter: The dose counter displays dose # 200
Appearance	QDP0014271	R+S	White to off-white powder for inhalation in a multi-dose powder reservoir device. Absence of external damage or powder leakage. Color of drug product formulation (by UV-vis): Complies with secondary standard (b) (4)%.
		R	A. By UPLC: Retention time of the drug peak in the sample is (b) (4)% of the corresponding retention time of drug standard.
Identification of the Drug Substances	QDP0014277	R	B. By TLC: The principal spot obtained in the sample has similar (b) (4) as the principal spot obtained from the reference solution.
		R	A. By UPLC: Retention time of the drug peak in the sample is (b) (4)% of the corresponding retention time of drug standard.
Assay (Total Drug Content per Inhaler)	QDP0014278	R+S	(b) (4) mg/Inhaler of Albuterol base

Chemistry Assessment Section

Release & Shelf Life Specifications (cont.)

<u>Test</u>	<u>Method</u>	<u>Use</u>	<u>Acceptance Criteria</u>
Aerodynamic Particle Size Distribution (APSD) by (b) (4)	QDP0015177	R+S	For n=5 inhalers perform determinations on each inhaler at beginning and end. Report mass deposition in 4 groups: Group 1 (MP/IP, Pre-Separator) (b) (4) µg Group 2 (Stage 1,2) (b) (4) µg Group 3 (Stage 3,4 & 5) (b) (4) µg Group 4 (Stage 6,7 & MOC) (b) (4) µg The mass balance is within (b) (4) % of label claim emitted dose for each individual test.
Water Content	QDP0014276	R+S	NMT (b) (4) % w/w
Microbiological Examination for Non-Sterile Products ³	QDP0015144	R+S	Total aerobic microbial count (TAMC): NMT (b) (4) CFU/g Total combined yeasts and moulds (TYMC): (b) (4) NMT (b) (4) CFU/g Pseudomonas aeruginosa: Absent/g Staphylococcus aureus: Absent/g Bile-tolerant Gram negative bacteria: Absent/g Escherichia coli: Absent/g

Release & Shelf Life Specifications (cont.)

<u>Test</u>	<u>Method</u>	<u>Use</u>	<u>Acceptance Criteria</u>
Dose Counter Reading	QDP0014705	R+S	After 30 actuations: # (b) (4) After 98 actuations: # (b) (4) After 180 actuations: # (b) (4) After 196 actuations: # (b) (4)
Number of Actuations per Inhaler	QDP0014655	R+S	Not less than 200 actuations
Foreign Particulates	QDP0043053	R+S	(b) (4) ≤ (b) (4) ≤ (b) (4) ≤ (b) (4) ≤ (b) (4)
Residual Solvents		R	Based on the manufacturer of the active ingredients/excipients statements and calculation as per USP <467> Option 1, product meets the USP <467> Residual Solvents limit criteria. No testing is required.

R – Release; S – Stability.

P.5.2 Analytical Procedures

Adequate.

Chemistry Assessment Section

(b) (4)

Expiration Period:

Teva is proposing a (b) (4) month expiration dating period for drug product, with the inhaler stored within its protective packaging, either in the upright or inverted orientation. The request is based on an analysis of real time accelerated stability data generated at 6 months and controlled room temperature stability data generated at 36 months for (b) (4) drug product batches. However, since the available real-time data from the (b) (4) batches only predict 24 months shelf life so far, with the supporting 36 months data from the (b) (4) batches, this reviewer considers a shelf life of 36 months more reasonable for the NDA approval.

The applicant is proposing an in-use period of 13 months. Based on an analysis of in-use stability data from 0 through 24 months storage, an expiry dating period of 13 months is supported, when the inhaler is stored horizontally without protective packaging (i.e. unwrapped).

Proposed Storage:

The drug product should be stored under controlled room temperature within protective foil packaging.

Once the foil packaging has been removed, the product is considered to be stable for 13 months when stored at room temperature (59°F to 77°F), avoiding extreme heat or cold.

Device orientation on storage has no pharmaceutically significant effect on product performance. The applicant proposes that the drug product will be packaged and transported in the inverted orientation in accordance with recommendations from study on the Effect of Simulated Shipping on Albuterol MDPI (see review under 3.2.P.2.4), which is acceptable.

Chemistry Assessment Section

(b) (4)

R REGIONAL INFORMATION
R1 Executed Batch Records

The executed batches records for the nine stability batches MD2001, 2003, 2004, AB 1001, 1002, 1004, 4001, 4002, and 4003 are provided. The batch records support the proposed commercial manufacturing process.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**A. Labeling & Package Insert**

The product name and strength should be revised to “Albuterol inhalation powder” and “97 µg.”

B. Environmental Assessment Or Claim Of Categorical Exclusion**Adequate.**

Teva requests a categorical exclusion pursuant to 21 CFR Section 25.31(b), as the FDA’s approval of this application will increase the use of the active moiety, but the estimated increase in the concentration of the substance at its highest level in the next 5 years at the point of entry into the aquatic environment will be below 1 part per billion.

Chemistry Assessment Section

Signature Page

Reviewer: Yong Hu, Ph.D., Office of New Drug Quality Assessment

Electronic Signature:

Yong Hu -S

Digitally signed by Yong Hu -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Yong Hu -S,
0.9.2342.19200300.100.1.1=2000336960
Date: 2015.01.22 16:40:05 -05'00'

Supervisor: Julia Pinto, Ph.D., Branch Chief, Office of New Drug Quality Assessment

Electronic Signature:

Julia C. Pinto -A

Digitally signed by Julia C. Pinto -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
cn=Julia C. Pinto -A, 0.9.2342.19200300.100.1.1=1300366849
Date: 2015.01.27 10:05:55 -05'00'

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

1. OMPQ Reviewer: Linda Ng, Ph.D.
2. NDA/BLA Number: 205-636
Submission Date: May 5, 2014
21st C. Review Goal Date: January 15, 2015
PDUFA Goal Date: March 15, 2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	ProAir RespiClick
Established or Non-Proprietary Name (USAN) and strength:	Albuterol Multi-Dose Dry Powder Inhaler
Dosage Form:	Dry powder inhaler

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	Teva Pharmaceutical
Responsible Organization (OND Division):	DPARP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

II. Application Detail

INDICATION: Treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise induced bronchospasm.

1. ROUTE OF ADMINISTRATION: Inhalation
2. STRENGTH/POTENCY: 90 mcg/dose, 200 doses
3. Rx/OTC DISPENSED: X Rx OTC
4. ELECTRONIC SUBMISSION (yes/no)? Yes
5. PRIORITY CONSIDERATIONS: No

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		X		
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult	X			
9.	Complex manufacturing	X			Manufacture of Dry Powder Inhalers
10.	Other (e.g., expedited for an unlisted reason)		X		

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
15.	Additional notes (non-filing issue)	X		
	1. Are all sites registered or have FEI #?			
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		X	

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?	X		New dosage form
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		(b) (4) has not been added
19.	From a CGMP/facilities perspective, is the application fileable? If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo X <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

Include process flow chart/diagram (see eCTD Section 2.3.S.1)

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?	X		

Include process flow chart/diagram (see eCTD Section 2.3.P.1)

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

Figure 1: Flow Chart Outlining the Manufacturing Process for Albuterol MDPI

(b) (4)

- 3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues. Nothing obvious**

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product.

The drug product manufacturing facility has never been inspected as an ADM facility. It is currently a testing facility CTL. See the Table for the rest of the facilities.

Additional information not covered above. None

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

Manufacturing Facilities Chart (generated from 602A DARRTS report and OMPQ macro):

NDA:	205636 Albuterol Sulfate Multi-Dose Dry Powder Inhaler											
Sponsor:	TEVA BRANDED PHARMACEUTICAL PRODUCTS R AND D INC											
Indication:	Treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise induced bronchospasm											
PDUFA:	3/5/2015 under STANDARD Review											
Responsible Organiz	CDER/ODEII/DPARP											
EERS Submitted By:	LIU, YOUBANG: CDER/ONDQA											
Chart Generated On:	6/11/2014											
						Overall OC Recommendation: PENDING entered into EES on 5/27/2014 2:08:09 PM						
						Reevaluation date:						
Establishment Name	EER Creation Date	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Firm Profiles - Current Status	Inspection History, Dates, Classifications	Facts Assignment Id	Most Recent Milestone	Most Recent EER Compliance	
TEVA PHARMACEUTICAL INDUSTRIES LTD.	5/27/2014	3003414719	ROW	ISR	Final manufacture, packaging, release and stability testing of commercial product	ADM	http://intranetapps.fda.gov/scripts/mpqa/profile.cfm?FEI=3003414719	AC as CTL, inspected 10/10/2013	9459237	ASSIGNED INSPECTION TO IB	PN	
(b) (4)												
(b) (4)												
TEVA PHARMACEUTICALS IRELAND	5/27/2014	3002807777	WEU	IRL	Amorphous Content Tes ing	CTL	http://intranetapps.fda.gov/scripts/mpqa/profile.cfm?FEI=3002807777	AC as ADM hat includes tes ing, inspected 9/12/2013		OC RECOMMENDATION	AC	
TEVA PHARMACEUTICAL INDUSTRIES	5/27/2014	3005202697	ROW	ISR	Test and release active ingredient, inactive ingredient, and container/closure	CTL	http://intranetapps.fda.gov/scripts/mpqa/profile.cfm?FEI=3005202697	AC for capsules and tablets, inspected 10/17/2013		OC RECOMMENDATION	AC	

For each EER, indicate PAI recommendation on the Manufacturing Facilities Chart above (e.g., PS, GMP, 10 Day, AC based on file review). This is the recommendation that will be entered into EES. **For PAI, include the reason for the PAI (i.e. PAI Trigger) in the comment section of the facilities chart.**

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) Yes
Based on Section IV, is a KTM warranted for any PAI? yes. If yes, please identify the sites in the above chart. Recommend KTM for Teva Pharmaceutical, Israel which has never been inspected as an ADM facility.
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) No
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL (DARRTS)

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

/s/

LINDA L NG
06/23/2014

VIPULCHANDRA N DHOLAKIA
06/23/2014

**ONDQA Initial Quality Assessment (IQA) ADDENDUM
For Pre-Marking Applications**

IQA ADDENDUM

1. NEW DRUG APPLICATION NUMBER: N205636

2. DATES AND GOALS:

Letter Date: 05-MAY-2014	Submission Received Date : 05-MAY-2014
PDUFA Goal Date: 05-MAR-2015	

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	ProAir® RespiClick® ¹
Established or Non-Proprietary Name (USAN):	Albuterol
Dosage Form:	Inhalation powder
Route of Administration	Oral inhalation
Strength/Potency	Undeclared ² /device delivers 108 mcg of albuterol sulfate from the mouthpiece (equivalent to 90 mcg of albuterol base)
Rx/OTC Dispensed:	Rx <input checked="" type="checkbox"/> OTC

4. INDICATION: For 1) treatment/prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease (asthma); 2) for the prevention of exercise-induced bronchospasm in patients 12 years of age or older. Albuterol sulfate is a short-acting β_2 -agonist bronchodilator already approved in other forms for the treatment of asthma.

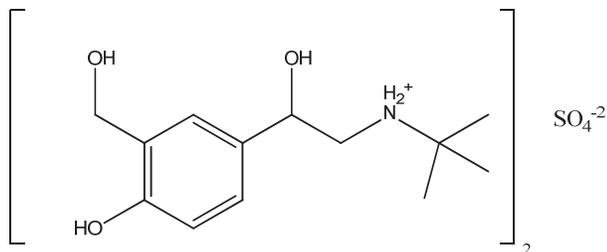
5. NAME OF APPLICANT (as indicated on Form 356h): Teva Branded Pharmaceuticals R&D, Inc.

6. DRUG SUBSTANCE STRUCTURAL FORMULA/DRUG PRODUCT:

¹ The device had previously been referred to as “(b) (4)” but the Agency did not agree with this proprietary device name.

² See correspondence of 06-MAY-2010.

**ONDQA Initial Quality Assessment (IQA) ADDENDUM
For Pre-Marking Applications**

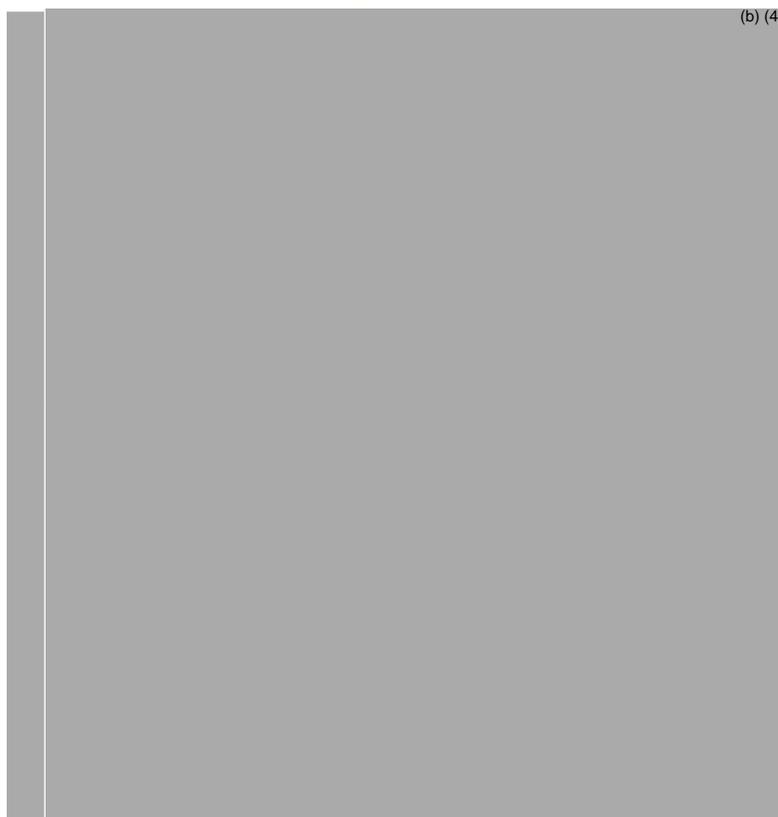


Albuterol Sulfate

The application is submitted in support of an albuterol sulfate inhalation powder drug product for the treatment of asthma. Note that while there are multiple single ingredient albuterol sulfate inhalation aerosols approved, there are no inhalation powder drug products (i.e., a new dosage form for albuterol). The device for this combination product is a reservoir type (device-metered) of inhalation product. The formulation in the reservoir is composed mainly of lactose monohydrate (b) (4) with (b) (4) of albuterol sulfate. A schematic drawing of the device is reproduced below from the application:

Start of Applicant Material

Figure 2: Cross Sectional View of the Primary Albuterol MDPI Device Sub-Assemblies



End of Applicant Material

**ONDQA Initial Quality Assessment (IQA) ADDENDUM
For Pre-Marking Applications**

Note that this addendum has been written to provide a more formal risk assessment to the reviewer regarding the drug product, which had not been required at the time the original IQA was written. The table below captures the associated risk analysis for each drug product CQA and is meant to help focus the reviewer on the higher risk aspects of the application during review.

**ONDQA Initial Quality Assessment (IQA) ADDENDUM
For Pre-Marking Applications**

DP attribute/ CQA	Factors that can impact the CQA ³	O ⁴	S ^{4,5}	D ⁴	FMECA RPN #	Comment & considerations
Delivered Dose Uniformity (DDU)	<ul style="list-style-type: none"> Inhomogeneity or low formulation assay of albuterol sulfate/lactose blend (e.g., from manufacturing; result of shipping) Lower than target fill of reservoir Failure of protective packaging (moisture ingress) Amorphous content of API Device malfunction Particle size/amorphous content of lactose Static charge of formulation 	2	2	2	8	<ul style="list-style-type: none"> DDU tested at release and for routine stability; small sample size (b) (4) Net content fill weight test; small sample size DP characterization study for exhaustion provided to assure sufficient reservoir overfill (b) (4) + 100% check weigh of filled inhalers (b) (4) 100% overwrap integrity IPC test 100% inhaler functionality test for first 3 actuations API tested for amorphous content at release 30°C/65%RH equilibration period to address triboelectrification prior to overwrapping Reference P.2.1 re: potential for amorphous lactose PSD of lactose specified
Aerodynamic Particle Size Distribution (APSD)	<ul style="list-style-type: none"> Inhomogeneity or low assay of albuterol sulfate/lactose blend Lower than target fill of reservoir Failure of protective packaging Particle size distribution of API Amorphous content of API Device malfunction Particle size/amorphous content of lactose 	2	2	2	8	<ul style="list-style-type: none"> APSD tested at release/stability; small sample size (b) (4) Net content fill weight test; small sample size DP characterization study for exhaustion provided to assure sufficient reservoir overfill + 100% check weigh of filled inhalers (b) (4) (b) (4) as per approved ProAir HFA® MDI of N21457 100% overwrap integrity IPC test 100% inhaler functionality test for first 3 actuations Device flow resistance is specified API tested for amorphous content/PSD at release

³ Based on underlying assumption that patients use the device as intended (human factors beyond scope of CMC evaluation).

⁴ O = Probability of Occurrence; S = Severity of Effect; D = Detectability

⁵ 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.

**ONDQA Initial Quality Assessment (IQA) ADDENDUM
For Pre-Marking Applications**

	<ul style="list-style-type: none"> Composition of device air flow path components Device flow resistance variation Static charge of formulation 					<ul style="list-style-type: none"> 30°C/65%RH equilibration period to address triboelectrification prior to overwrapping Reference P.2.1 re: potential for amorphous lactose PSD of lactose specified (b) (4)
Purity (impurities/degradants)	<ul style="list-style-type: none"> degradation of API as formulated input purity of API input purity of lactose 	1	2	2	4	<ul style="list-style-type: none"> Dry powder less susceptible to degradation than liquid based formulations API compatibility with lactose and device reservoir component can be evaluated based on drug product stability data (total impurities slightly trend with time) API already approved for use for inhalation product of N21457 (b) (4) lactose grade not evaluated, but supplier approved for other grades for inhalation products

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page!

Craig M. Bertha, PhD
Acting CMC-Lead
Division III
Office of New Drug Quality Assessment

{See appended electronic signature page!}

Eric Duffy, PhD
Acting Branch Chief/Division Director
Division III
Office of New Drug Quality Assessment

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

/s/

CRAIG M BERTHA
06/13/2014

ERIC P DUFFY
06/13/2014

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

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: N205636

2. DATES AND GOALS:

Letter Date: 05-MAY-2014	Submission Received Date : 05-MAY-2014
PDUFA Goal Date: 05-MAR-2015	

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	ProAir® RespiClick® ¹
Established or Non-Proprietary Name (USAN):	Albuterol
Dosage Form:	Inhalation powder
Route of Administration	Oral inhalation
Strength/Potency	Undeclared ² /device delivers 108 mcg of albuterol sulfate from the mouthpiece (equivalent to 90 mcg of albuterol base)
Rx/OTC Dispensed:	Rx <input checked="" type="checkbox"/> OTC

4. INDICATION: For 1) treatment/prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease (asthma); 2) for the prevention of exercise-induced bronchospasm in patients 12 years of age or older. Albuterol sulfate is a short-acting β_2 -agonist bronchodilator already approved in other forms for the treatment of asthma.

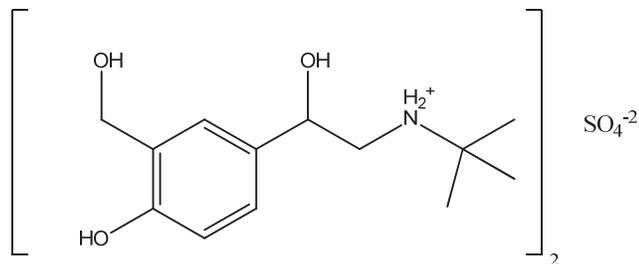
5. DRUG SUBSTANCE STRUCTURAL FORMULA:

¹ The device had previously been referred to as (b) (4) but the Agency did not agree with this proprietary device name.

² Note that the applicant was informed in the correspondence of 06-MAY-2010, that:

“The strength of the product will need to correspond to the metered dose, (b) (4). Thus reference to ‘Label Claim’ technically refers to the metered target dose for inhalation powder drug products. Revise the various acceptance criteria that involve reference to the emitted dose target such that ‘Label Claim’ is substituted with a more appropriate term (e.g., Label Claim Emitted Dose or LCED).” The absence of a defined “metered dose” may result in labeling discrepancies versus other similar drug products.

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



Albuterol Sulfate

6. NAME OF APPLICANT (as indicated on Form 356h): Teva Branded
Pharmaceuticals R&D, Inc.

7. SUBMISSION PROPERTIES:

Review Priority:	Standard Priority
Submission Classification (Chemical Classification Code):	Based on draft MaPP 7500.3, Type 3: New Dosage Form
Application Type:	505(b)(2)
Breakthrough Therapy	Yes No <u>X</u>
Responsible Organization (Clinical Division):	DPARP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	Drug product expiration dating period is based on real time stability data; Although not an NME, reviewer should consider the principles outlined in ICH Q1E when evaluating the applicant's proposed expiration dating period and stability data.
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		The ONDQA PM entered the EER in EES on 27-MAY-2014

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Pharmacology/Toxicology	X		<p>It is unlikely that a consult to the pharmacology/toxicology group will be necessary as the albuterol sulfate (DMF (b) (4)) is already found acceptable for use in inhalation drug products and the lactose (b) (4) is being sourced from a supplier that has been used by other applicants for approved inhalation powder drug products, albeit, under other master files.</p> <p>However, it is noted that we “encouraged” the sponsor at the CMC EOP2 meeting and at the 05-OCT-2010, EOP2 meeting to reduce the allowance of the levels of the (b) (4) impurity and referred them to the draft guidance on genotoxic and carcinogenic impurities. Currently the limit for (b) (4) in the drug product is not more than (u) (4)% (with 12 actuations this would equate to a maximum of (b) (4) mcg of (b) (4) per day. Consult with the pharm/tox team regarding the acceptability of this limit.</p>
Methods Validation			It will be left to the reviewer to decide if it is warranted to send any methods for assessment by the Agency laboratory, based on evaluation of the method and the associated validation data provided.
Environmental Assessment			The applicant claims categorical exclusion as per 21 CFR 25.31(b). The reviewer can consult with the OPS EA expert (R. Bloom, PhD) if the calculations related to the expected introduction concentration are determined to be questionable.
CDRH			The DPARP PM has sent a consult to CDRH dated 28-MAY-2014, regarding the human factors study report included in P.2 of the application. From a purely CMC-perspective, it is not necessary at this point to request CDRH to evaluate any of the quality-related information for the device, however, this may change once a detailed evaluation is performed by the reviewer (if NDA is filed).
Other			N/A

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

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes <input checked="" type="checkbox"/> No
CMC Filing Issues: Currently the application does not include a letter of authorization from the device manufacture to allow our review of a DMF that contains pertinent CMC information for the device. It appears that the device manufacturer (b) (4) had a DMF (b) (4) for the (b) (4) inhaler, but that due to inactivity, the file was closed in 2013. An information request regarding this filing issue was sent to the firm on 03-JUN-2014. However, the applicant has indicated that they own the device and all of the associated technology such that any questions regarding the CMC information for the device can be directed to the applicant directly.

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes <input checked="" type="checkbox"/> No
CMC Comments for 74-Day Letter (assuming filing): 1. Provide data to support the label claim strength of the drug product for the label/labeling. We remind you of our communication dated May 6, 2010, where we had informed you that the strength of the product should correspond to the metered dose, not the amount of drug emitted from the mouthpiece.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes <input checked="" type="checkbox"/> No
Biopharmaceutics Filing Issues: 1.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes No <input checked="" type="checkbox"/>
Biopharmaceutics Comments for 74-Day Letter: 1.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes <input checked="" type="checkbox"/> No
Microbiology Filing Issues: See memorandum dated 29-MAY-2014 from Bryan S. Riley, PhD. The microbiology team recommends that the application be approved (and presumably filed).

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

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	N/A

Is a team review recommended?	Yes	No	X
Suggested expertise for team:			

Summary of Critical Issues and Complexities: See the summary list below at the beginning of the IQA review.

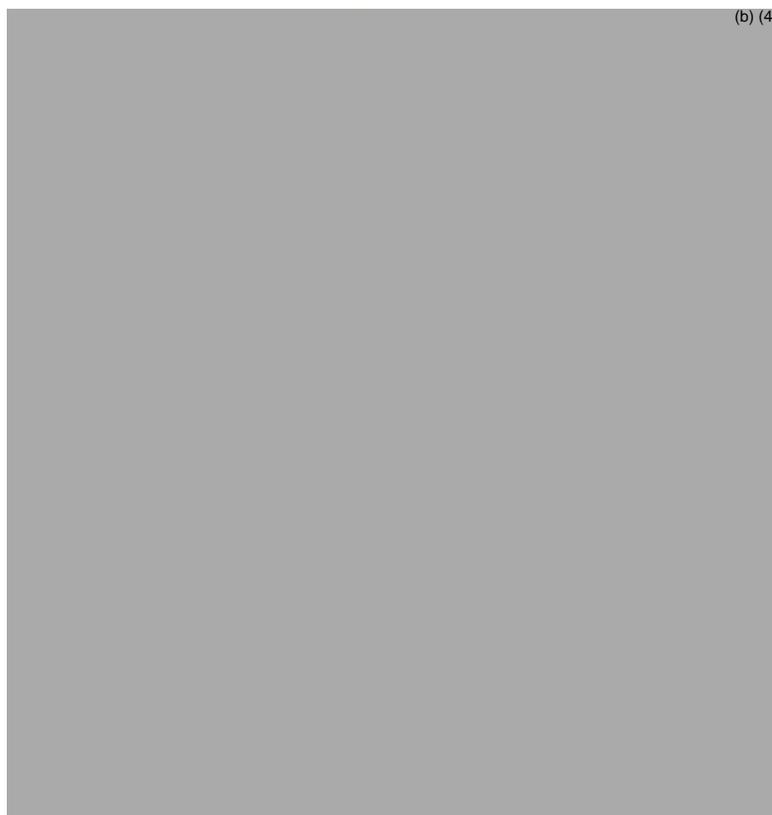
**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

INITIAL QUALITY ASSESSMENT

The application is submitted in support of an albuterol sulfate inhalation powder drug product for the treatment of asthma. Note that while there are multiple single ingredient albuterol sulfate inhalation aerosols approved, there are no inhalation powder drug products (i.e., a new dosage form for albuterol). The device for this combination product is a reservoir type (device-metered) of inhalation product. The formulation in the reservoir is composed mainly of lactose monohydrate (b) (4) with (b) (4) mg of albuterol sulfate. A schematic drawing of the device is reproduced below from the application:

Start of Applicant Material

Figure 2: Cross Sectional View of the Primary Albuterol MDPI Device Sub-Assemblies



End of Applicant Material

In addition to the lack of information regarding the manufacturing of the (b) (4) device as noted above, below are a list of critical issues and complexities that have been noted during development (under IND 104532) or observed in the cursory IQA/filing review that should be taken into consideration during the evaluation of the application, assuming it is filed:

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

- As noted above, there does not appear to be any data supporting the label claim strength of the drug product in the application (see filing letter comment above).
- We had requested that the applicant include a test for amorphous content for the lactose excipient. They indicate in P.4.4, that amorphous content will not be tested for the lactose, and they have provided data to support a justification that will need to be evaluated.
- Routine extractables controls for device components are described in P.7 and will need to be evaluated to assure they serve the purpose intended.
- The Agency had requested that the applicant include appropriate tests with acceptance criteria for those dimensions of the device that would be critical to the reproducible metering and delivery of the drug product formulation. The specifications for the various device components appear to be limited in terms of dimensional requirements (and there is no associated DMF from the device manufacturer). An evaluation of the adequacy of the specifications should consider assurance of dosing reproducibility during the shelf life of the drug product.
- The proposed acceptance criterion for the fine particles of drug collected on stages 3-5 of the (b) (4) impactor for APSD individual determinations is (b) (4) mcg. This range of (b) (4) fold is somewhat larger than the “rule-of-thumb” limit of (b) (4) fold that the Agency has typically recommended for similar drug products. The reviewer may need to seek input from the clinical team regarding the acceptability of these limits if the data do not support tightening of the criterion. Note that the applicant is testing n = 5 inhalers at beginning and end and mass balance criterion for each determination is in line with Agency recommendations ((b) (4) % of label claim emitted dose).
- As indicated above, it does not appear that the applicant has characterized the metered dose of the drug product, which also relates to potential dose hold-up or build-up. In the drug product characterization section it is claimed that no cleaning is necessary during patient use.
- The applicant appears to have provided drug product characterization data supporting the ruggedness (effect of dropping, shaking, simulated shipping, etc.) and impact of use in different orientations, as was addressed at the 27-MAR-2009, meeting during development.
- The applicant has provided in-use data (after overwrap removed and under intermediate storage conditions of 30°C/65%RH) as requested by the Agency during development. And, as also requested due to the unique design, the applicant has provided data characterizing drug product performance with the mouthpiece left open both prior to dose delivery and after dose delivery. These studies are in the P.2 section of the application.
- The sponsor was sent responses to multiple CMC-related questions posed at end-of-phase 2 (06-MAY-2010, correspondence). The advice and recommendations provided were in

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

line with the current policy and practice in place at the time for DPI drug products. As a result, the sponsor cancelled the CMC EOP2 meeting. A few issues are worth noting:

- The sponsor was informed that they should incorporate counter accuracy and reliability assessment during any “through life” performance testing that takes place at release, for stability samples, for drug product characterization studies, or for drug product returned from the clinical site (both complaint devices and routine returns). It is important that the dose counter have sufficient accuracy and reliability to meet the clinical expectations. The reviewer may need to discuss the counter-related data with the clinical reviewer if it appears to be marginally acceptable or otherwise problematic.
- Note that the applicant currently has a single set of APSD acceptance criteria for the (b) (4) Impactor testing of the drug product at the beginning and end of inhaler life (through life). We had indicated that if there were a significant beginning-to-end trend in APSD, separate acceptance criteria may be necessary for the two life stages. The reviewer should keep in mind this advice we gave to the sponsor at the EOP2 when evaluating the APSD through life data.
- The Office provided the sponsor with comments on their approach to the handling of APSD mass balance failures. Refer to the Agency comments when reviewing the current proposed protocol.
- We reminded the sponsor that they would need to characterize the stability of the drug product with-out the protective packaging for a length of time twice that of the proposed in-use period. This should be considered when evaluating the in-use stability data. Also, at the subsequent pre-NDA meeting held on 19-NOV-2013, we asked that the applicant also consider potential *pro re nata* usage of the drug product when conducting their in-use studies. This is important considering that some patients do not use albuterol regularly or daily.
- The sponsor was asked to also examine simulated use that would mimic dose emission from the device if the patient were in the supine position. This had not been included in the proposed protocol presented at EOP2. Such data will be important to support the patient instructions for use.
- The Agency questioned the proposals for the justification of the reservoir fill weight. The reviewer should assure that the extremes of the allowed fill weight range are justified with data.
- In 2012 the Division became aware that the sponsor had observed a patient mis-use issue in the clinical studies, and as a result they made several device modifications to address such mis-use. Refer to the CMC review dated 04-MAR-2013, prior to review of the application, for details and evaluation.

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

- At the 19-NOV-2013, meeting, we agreed to accept updated stability data for 3 batches of the drug product manufactured (b) (4) at the commercial site, which would be in addition to other stability data from that site for product from the (b) (4)
- The applicant has submitted comparability protocols in P.2.4, as outlined in the cover letter of the NDA, regarding changes to drug device components (b) (4) and site changes for device manufacturing. We had agreed to accept and evaluate these protocols at the 19-NOV-2013, pre-NDA meeting.
- Drug product characterization studies are included in section P.2.4 of the application, along with detailed information pertaining to the device. These should be evaluated to support labeling and patient instructions.

BIOPHARMACEUTICS INITIAL ASSESSMENT

Biopharmaceutics Summary

Albuterol Multi-dose Dry Powder Inhaler (Albuterol MDPI) Inhalation Powder product contains a formulation of albuterol sulfate and lactose monohydrate, delivering 90 mcg of albuterol base from the inhaler mouthpiece at each actuation. It is proposed to be used for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

The clinical program consisted of 8 clinical studies: a cumulative dose Phase 1 study, a 5-way single-dose Phase 2 dose-ranging study and 5 Phase 3 studies that included 3 pivotal efficacy studies.

A Chemistry, Manufacturing and Controls (CMC) program has been conducted for the product including a stability program on nine exhibit batches. Based on the testing at various orientations and conditions, as well as in- and out-of-package testing, the Applicant is proposing (b) (4) months expiry for the packaged product and 13 months expiry for the out-of- package product. Full details are in 3.2.P.8.1 Stability Summary and Conclusions. Key CMC reports are in Section 3.2.P.2 Pharmaceutical Development:

- Report on the Results of Human Factors Testing (Section 3.2.P.2.4, Container Closure System – Human Factors Study Report)
- A total of 15 Drug Product Characterization Studies, including a Spacer Study, as recommended by the Agency (Section 3.2.P.2.4, Container Closure System – Drug Product Characterization)
- Two comparability protocols: the first for (b) (4) for one of the components; the other for an alternate site of manufacture of the device (Section 3.2.P.2.4, Container Closure System).

The two comparability protocols are summarized below.

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

1. [REDACTED] (b) (4)

The Applicant has been notified that commercial supply of [REDACTED] (b) (4) is being discontinued. It is therefore proposed to replace the [REDACTED] (b) (4) with an alternative [REDACTED] (b) (4). The alternative material will be chosen to have similar characteristics and performance to the existing material.

The change to an alternative material grade has been risk assessed as low risk. The alternative material will undergo a [REDACTED] (b) (4) qualification program. Albuterol MDPI devices will be manufactured using [REDACTED] (b) (4). These will undergo full batch release testing of sub-assemblies, they will be filled with drug formulation and will undergo full finished product release testing.

Upon prior agreement with FDA, the material change will be communicated to FDA through a CBE-30 Supplement with a comparability report based on original and new material batch release testing and finished product release testing.

A detailed comparability protocol for this material change is in Section 3.2.P.2.4 [REDACTED] (b) (4)

2. Second Device Manufacturing Site

The exhibit and clinical batches of Albuterol MDPI used devices manufactured from sub-assemblies that had been [REDACTED] (b) (4) at [REDACTED] (b) (4). To meet the anticipated volume demands for Albuterol MDPI, a second manufacturing site for the device sub-assemblies is being developed at [REDACTED] (b) (4). This site will carry out comparable [REDACTED] (b) (4) test and release activities to those currently undertaken at the [REDACTED] (b) (4) site. It is proposed that devices manufactured at the new site and subsequently filled with drug formulation will undergo finished product release testing and be placed on a stability program.

Upon prior agreement with FDA, the supply of commercial devices from the new site will be communicated to FDA through a CBE-30 supplement with a comparability report based on original and new manufacturing site batch release testing, finished product release testing and results from a minimum of six months stability testing.

A detailed comparability protocol for this second manufacturing site is in Section 3.2.P.2.4 'Comparability Protocol for Second Device Manufacturing Site'.

Critical Review Issues

Critical review issues identified during filing are as follows.

- The suitability of the comparability protocol for the proposed changes.

Comments for Day 74-Letter

None

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

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		For the pages that were examined for this IQA review.
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		See details outlined above.

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	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? This question is not applicable for synthesized API.			NA

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

	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		DMF (b) (4)
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		

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

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • 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		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		A categorical exclusion is requested as per 21 CFR 25.31(b).

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

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			Reference is made to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Reference is made to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?			Reference is made to DMF (b) (4)
15.	Does the section contain controls for the DS?			Reference is made to DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?			Reference is made to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			Reference is made to DMF (b) (4)
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			Reference is made to DMF (b) (4)

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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		See P.2
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		Note that the final device is the (b) (4) and that an earlier version was (b) (4) (supportive stability data are provided with the latter device).
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			Although the applicant uses some QbD related terminology and has performed some DoE experiments to support some of their manufacturing processes, none of this information appears to be used for revising the drug product control strategy for “regulatory relief.”
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

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F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		X	If the reviewer determines that it is prudent to send one or more methods to the Agency lab for assessment, a request for sample information can be made of the applicant. Other pertinent information typically provided in a MV package are found in various locations within the NDA.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product		X	

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?		X	There is no DMF letter of authorization allowing review of information on the manufacture of the (b)(4) device (now referred to as "RespiClick") by (b)(4) (DMF (b)(4)). It appears that this DMF was inactive and has subsequently been closed. However, in an electronic mail message from the applicant dated 04-JUN-2014, they indicate that they own the device and all associated technology. Thus, any requests for additional device-related information or data can be made directly to the applicant.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b)(4)	2	[REDACTED]	(b)(4)	16-APR-2013	Found adequate to support an inhalation solution drug product 17-MAR-2011; ARs submitted subsequently
	4			02-MAY-2013	(b)(4)
	3			21-JAN-2014	Unclear from DARRTS if reviewed for this particular (b)(4)

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(b) (4)	3	(b) (4)	20-JUL-2013	Unclear from DARRTS if reviewed for this particular (b) (4)
	3		26-APR-2013	DMF not reviewed

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

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The following parameters for the ONDQA’s Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	YES	NO	COMMENT
34.	Does the application contain dissolution data?		X	NA
35.	Is the dissolution test part of the DP specifications?		X	
36.	Does the application contain the dissolution method development report?		X	
37.	Is there a validation package for the analytical method and dissolution methodology?		X	
38.	Does the application include a biowaiver request?		X	
39.	Does the application include an IVIVC model?		X	
40.	Is information such as BCS classification mentioned, and supportive data provided?		X	
41.	Is information on mixing the product with foods or liquids included?		X	
42.	Is there any <i>in vivo</i> BA or BE information in the submission?	X		A Phase 1 study with accumulative dose was conducted. The study will be reviewed by OCP.
43.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping?		X	

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B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
44.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
45.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable.
46.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page

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

/s/

CRAIG M BERTHA
06/05/2014

JOHN Z DUAN
06/05/2014

TAPASH K GHOSH
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