CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207921Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 207921
Review #1

Drug Name/Dosage Form	QVAR® Redihaler (beclomethasone dipropionate) Inhalation Aerosol[1]
Strength	40, 80 mcg/actuation
Route of Administration	Oral inhalation
Rx/OTC Dispensed	Rx
Applicant	Norton (Waterford) Ltd.
US agent, if applicable	Teva Branded Pharmaceutical Products R&D Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*03-Oct-2016*	*All*
Amendment	*04-Oct-2016*	*Facilities*
Amendment	*23-NOV-2016*	*Drug product, process, microbiology*
Amendment	*07-DEC-2016*	*Facilities, drug substance*
Amendment	*17-JAN-2017*	*Drug product*
Amendment	*27-JAN-2017*	*Drug product*
Amendment	*02-MAR-2017*	*Process, microbiology*
Amendment	*26-MAY-2017*	*Process*
Amendment	*14-JUN-2017*	*Drug product*
Amendment	*21-JUN-2017*	*Drug product*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Debasis Ghosh	NDBII/DNDAPI
Drug Product	Venkat Pavuluri	DNDPII/NDPIV
Process	Brian Rogers	DPAII/PABIV
Microbiology	Daniel Schu	DMA/MABIII

[1] The Redihaler is a breath-actuated version of the QVAR press-and-breathe inhalation aerosol (or metered dose inhaler or MDI) of NDA 20911.

Facility	Aditi Thakur	DIA/IABII
Biopharmaceutics	N/A	DB/BBII
Regulatory Business Process Manager	Florence Aisida	DRBPMI/RBPMBI
Application Technical Lead	Craig M. Bertha	DNDPII/NDPIV
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
4871	Type II	Teva Pharmaceutical Industries Ltd.	Beclomethasone dipropionate (BDP)	Adequate	12-JAN-2017	
(b) (4)	Type III		(b) (4)	Adequate	30-MAR-2017	
	Type III			Not reviewed		Adequate information in NDA
	Type III			Adequate	22-APR-2016	
	Type III			Not reviewed		Adequate information in NDA
	Type III			Not reviewed		Adequate information in NDA
	Type III			Not reviewed		Adequate information in NDA
	Type IV			Adequate	08-FEB-2016	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20911	Qvar (beclomethasone dipropionate) Inhalation Aerosol
NDA	202813	Qnasl (beclomethasone dipropionate) Nasal Aerosol
IND	114865	Beclomethasone dipropionate inhalation aerosol
IND	(b) (4)	

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

The application is recommended to be **approved** from the quality perspective. All sub-disciplines (drug substance, drug product, process, microbiology, and facilities) concur that the quality aspects of the drug product, as manufactured, meet the standards expected for an inhalation drug product for the intended patient population.

Currently, and 18 month expiration dating period is granted for both strengths of the drug product.

II. Summary of Quality Assessments

A. Product Overview

The QVAR® Redihaler is a breath-actuated version of the applicant's QVAR Inhalation Aerosol. It provides beclomethasone dipropionate (BDP) corticosteroid for inhalation for prophylactic therapy of patients, 4 years and older, with asthma, but is not indicated for acute bronchospasm. Relative to a typical press-and-breathe inhalation aerosol, a breath-actuated inhalation aerosol removes the need for patients to coordinate their inhalation breath with the actuation of the device valve to dispense a dose of formulation, with the intent being less variable dose delivery to the patients' lungs.

Proposed Indication(s) including Intended Patient Population	"Beclomethasone dipropionate BAI is indicated in the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. (b) (4) [redacted]
Duration of Treatment	Chronic
Maximum Daily Dose	320 mcg BID (8 @ 80 mcg actuations)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

The drug substance for this (solution formulation) inhalation aerosol is beclomethasone dipropionate (BDP), which is a USP monographed compound. The CMC information for drug substance is referenced to DMF 4871, which was found to be adequate to support the NDA. BDP has eight chiral centers, and it is slightly soluble in water. (b) (4) which is a related degradant of BDP, is the only impurity observed in the active pharmaceutical ingredient (API) at release. All other BDP related substances are considered unspecified impurities and controlled at NMT (b) (4)%. (b) (4) impurities are controlled as per ICH guidance recommendations. Potential mutagenic impurities include (b) (4) The (b) (4) impurity is controlled at NMT (b) (4)% where the allowed limit based on the maximum daily dose of (b) (4) mcg and the threshold of toxicological concern of (b) (4) mcg is (b) (4)%. Possible (b) (4) from six batches showed (b) (4) ppm or (b) (4) times lower than the permitted amount. The BDP retest period is (b) (4) months and there is also an expiration period of (b) (4) months from the date of receipt or manufacturer's expiration date, whichever is earlier. The drug substance manufacturing facility (b) (4) has received an approval recommendation, as does the API (b) (4) site (b) (4)

QVAR® Redihaler, Beclomethasone dipropionate (breath-actuated) inhalation aerosol (BDP BAI) is presented in two dosage strengths intended to deliver either 40 mcg per actuation or 80 mg per actuation (ex-actuator) and a minimum of 120 actuations each, with strengths distinguished by the color of the BAI device. BDP BAI is a solution formulation of beclomethasone dipropionate (BDP) in (b) (4) and 1,1,1,2-tetrafluoroethane (also referred as HFA-134a) as propellant, contained in a (b) (4) aluminum canister closed with a primeless metering valve of 50 microliters (mcL) (b) (4), and fitted into a breath-actuated inhaler (BAI). Inhalers are individually packed with a patient information leaflet and information for use leaflet into a paper carton. The BAI device, constructed of two sub-assemblies, the Force Holding Unit (FHU) and the Main Body Assembly (MBA), synchronizes the dispensing of metered dose with patient inhalation, eliminating the need for patients to co-ordinate inhalation with the manual actuation of an aerosol canister.

(b) (4)

(b) (4) microorganisms. The drug product manufacturing

facility (IVAX Pharmaceuticals Ireland) and [redacted] have received approval recommendations and the CDRH Office of Compliance has recommended post-approval inspection of the two device-related manufacturing and control facilities (Norton Waterford Ltd. and Teva Branded Pharmaceutical Products R&D Inc.).

Apart from the typical quality control information and data evaluated in support of this drug product, there were several device-related problems that were observed during development, either by analysts during testing, or via patient complaints during the clinical studies. First, the applicant had problems with the device [redacted] during development. [redacted]. The applicant and valve manufacturer made changes [redacted] during development to address this issue, and improvement was realized [redacted] However, the applicant agrees to monitor the first three commercial scale batches after storage at all ICH Q1A storage conditions, such that there will be additional data available to gauge their corrective action for the [redacted] manufacturing. In addition, the applicant has revised the drug product test methods to assure analysts perform a thorough examination for any evidence of [redacted] Second, there were patient complaints (about 1.0% rate) of devices actuating prematurely, and this was traced to variability in placement of the [redacted] of the device. As a result, the applicant has taken corrective action to orient and inspect for the proper placement of this part during [redacted] manufacture. Third, there were complaints (about 0.5% rate) of the [redacted] Fourth, there were some complaints regarding the counter devices, but the same counter mechanism is used in the press-and-breathe QVAR Inhalation Aerosol, and since the complaint rate is less than 0.002% (over [redacted] units dispensed), thus no changes to the counter are proposed currently. In summary, although not desirable, it is not unexpected for there to be some minor changes to these types of devices, based on testing observations and patient complaints during clinical studies. The applicant has been diligent in addressing these to provide greater assurance of the quality of the commercial drug product they plan to market. Nevertheless, during life-cycle management of this application, it will be prudent for the Agency to monitor annual and any field-alert reports for additional quality issues that may only become evident with wide-spread use.

From a risk/benefit perspective, the advantage of a breath-actuated inhalation aerosol to the patient, relative to a typical press-and-breathe inhalation aerosol, i.e., the elimination of the coordination of actuation and inhalation, is likely worth the increased complexity of the former over the latter device, as the applicant has demonstrated a willingness to address and correct human factor-related issues that had been observed with patient use.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

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

LABELING

For NDA 207921

R Regional Information

1.14 Labeling

Immediate Container Label (Trade and Professional Samples)

Note: Based on the Drug product packaging configuration, where the canister is combined with the breath actuated device the label places on the actuator is deemed as the immediate container label.

Start of sponsor material

End of sponsor material

The manufacturer and distributor details were listed as per 21 CFR 201.1. The NDC code was included as suggested by 21 CFR 201.2. The name of drug substance was listed as part of the established name as per 21 CFR 201.10 and the strength (for the two dose strengths) was given as per 21 CFR 201.100(b)(4) in terms of the amount of active component, delivered ex-actuator. The strength of drug product included (i.e. 40 mcg or 80 mcg as applicable) was the amount delivered ex-actuator. The statement "Rx only" is included as per 21 CFR 201.100(b)(1). The net quantity of contents was provided as per 201.51. It was noted that the label also instructs the patient when to replace the drug product (combined with the breath actuated device). The storage conditions listed were consistent with the package insert, which is acceptable based on the stability data evaluated from section 3.2.P.8. The expiration date has a place on the label as per 21 CFR 201.17. There are also instructions as per 21 CFR 201.5 for use preparation (i.e., "Close cap after each actuation").

In addition to the common text on the labels of trade and professional samples, the label for professional sample also has the statement "**Professional Sample. Not for Sale**"

Reviewer's Assessment: Acceptable. The labels (for two dosage strengths, trade and professional samples) have all required information from CMC perspective.

Immediate container labels (Actuator label) for the two strengths are similar in layout, except for the dosage strength designation. The two dosage strengths are differentiated by color scheme used for the labels matching to the external colors of the respective device components (FHU and MBA). The label text include route of administration, NDC number, proprietary name and established name for the active ingredient, dosage form type and strength, suggested storage conditions, names of the manufacturer and distributor and essential directions for using the inhaler (Close cap after each use) that are necessary (b) (4) for the next dose.

Carton

Start of sponsor material

(b) (4)

End of sponsor material

The text of the cartons meets the requirements for Proprietary name, established name (font size and prominence) [per FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21

CFR 201.10(g)(2)], Strength [21CFR 201.10(d)(1); 21.CFR 201.100(b)(4)], Net contents (21 CFR 201.51(a)), Lot number per 21 CFR 201.18, Expiration date per 21 CFR 201.17, "Rx only" statement per 21 CFR 201.100(b)(1), Storage Conditions, NDC number (per 21 CFR 201.2), Bar Code per 21 CFR 201.25(c)(2), Name of manufacturer/distributor, "Read package insert for Prescribing information" (21 CFR 201.55), "Keep out of reach of children" (optional for Rx), Route of Administration (21 CFR 201.100(b)(3)) and Quick Guide to patients / care givers.

Reviewer's Assessment: Acceptable. The cartons (for two dosage strengths, trade and professional samples) have all required information from CMC perspective.

The cartons for the two strengths are similar in layout, except for the dosage strength designation and color scheme, where bottom of the carton and back ground of the strength designation for the cartons was matched with the external colors of the respective device components (FHU and MBA). The carton text include NDC number, proprietary name and established name for the active ingredient, dosage form type and strength, route of administration, storage conditions, directions for use (Quick Guide and reference to the patient instructions inside the carton).

In addition to the common text on the carton of trade and professional samples, the carton for professional sample also has the statement "Professional Sample. Not for Sale"

List of Deficiencies: None

Primary Labeling Reviewer Name and Date: Venkateswara R. Pavuluri, Ph.D.; R. Ph.; Jun 26, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Julia C. Pinto, Ph. D.;

Venkateswara Pavuluri

Digitally signed by Venkateswara Pavuluri
Date: 6/26/2017 04:02:12PM
GUID: 551eb409003b6d46b8d5dfa7699e4742

Julia Pinto

Digitally signed by Julia Pinto
Date: 6/26/2017 04:04:31PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

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

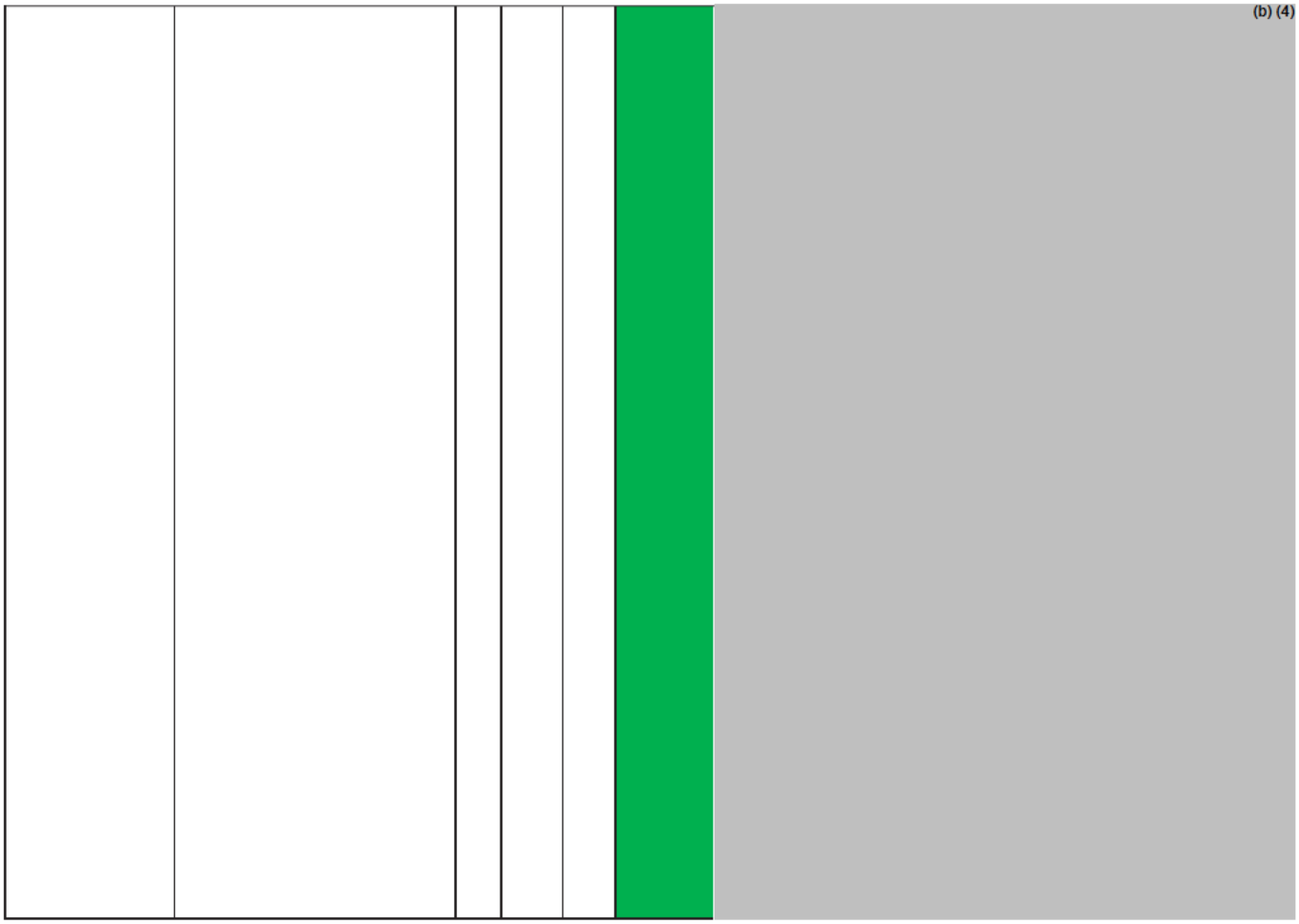
Attachment - Final Risk Assessment

DP attribute/ CQA	Factors that can impact the CQA[1]	O[2]	S[2,3]	D[2]	FMECA RPN #	Comment & considerations
Delivered Dose Uniformity	(b) (4)	3	3	2	18	(b) (4)

[1] Patient mis-use can impact performance of device but human factors are beyond scope of CMC evaluation

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

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


(b) (4)

						(b) (4)
Aerodynamic Particle Size Distribution (APSD)	(b) (4)	3	3	2	18	
Spray Pattern (see (b) (4)		2	3	4	24	

Craig
Bertha

Digitally signed by Craig Bertha
Date: 6/28/2017 07:34:53AM
GUID: 50841a65000098a9383c817879a6a84d

MICROBIOLOGY

Product Background:

NDA: 207921

Drug Product Name: QVAR REDIHALER (Beclomethasone dipropionate), 40 µg, 80 µg

Route of Administration: Oral inhalation

Applicant Name: Norton (Waterford) Limited

Manufacturing Site: IVAX Pharmaceuticals Ireland (aka Teva Pharmaceuticals Ireland)
IDA Industrial Park
Cork Road, Waterford
Ireland

Method of Sterilization: The drug product is non-sterile.

Review Summary: Adequate
The drug product is non-sterile. The submission demonstrates that adequate controls are in place for manufacturing of the drug product; therefore, it is recommended for approval on the basis of product quality microbiology.

List Submissions being reviewed: Seq 0001: 03 October 2016 (original submission); Seq 0013: 02 March 2017 (response to Microbiology Information Request)

Supporting/Related Documents: N/A.

Remarks Section: The submission was provided in the eCTD format.

S Drug Substance- N/A.

Reviewer's Assessment: The drug substance manufacturing process is not the subject of this product quality microbiology review as the finished drug product is non-sterile.

P.1 Description of the Composition of the Drug Product

- **Description of drug product** –
  (See Seq 0001, Section 3.2.P.1, *Description and Composition of the Drug Product.pdf*)

  QVAR REDIHALER (proposed), Beclomethasone dipropionate HFA breath-actuated inhalation aerosol (BDP BAI) is for oral inhalation and indicated for the maintenance treatment of asthma as prophylactic therapy.

- **Drug product composition** –
  (See Seq 0001, Section 3.2.P.1, *Description and Composition of the Drug Product.pdf*)

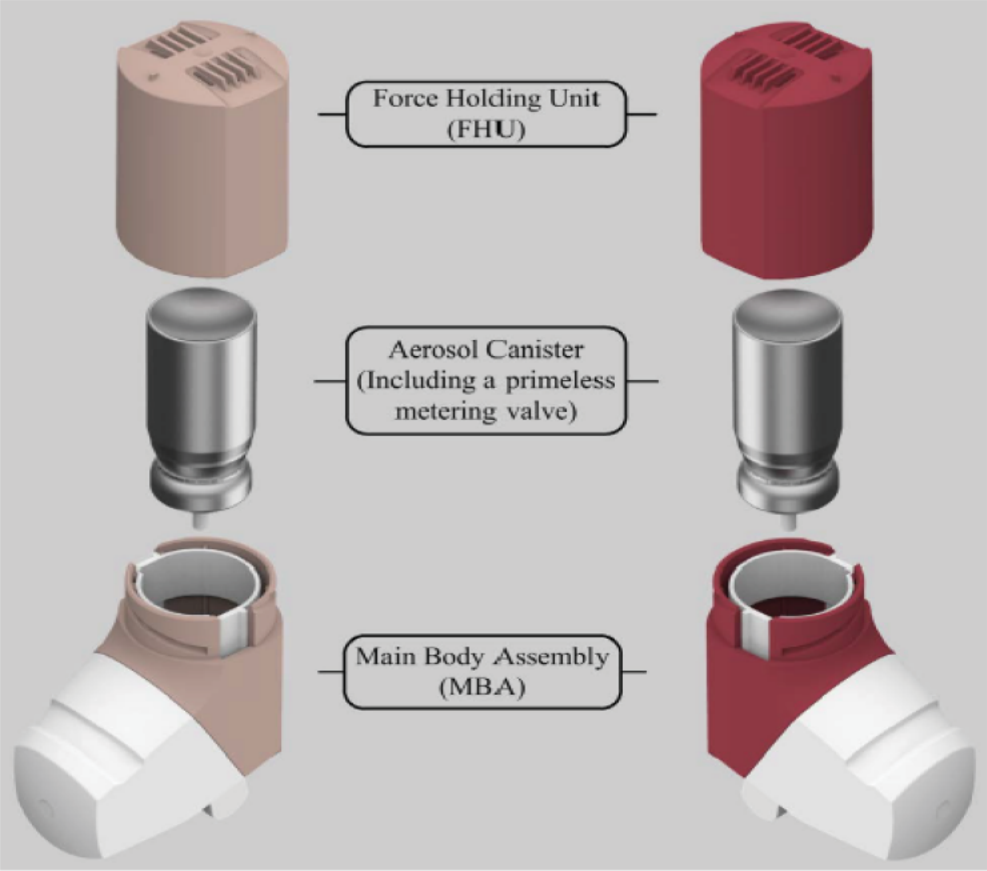
  Two strengths of the drug product were developed that deliver 40 µg per actuation and 80 µg per actuation of the API. The following table is provided for the composition of the two strengths of the drug product.

Ingredient	Function	Quantity per container for BDP BAI 40 µg (g)	Quantity per container for BDP BAI 80 µg (g)
Beclomethasone dipropionate	Active ingredient		(b) (4)
HFA-134a	Propellant		
Target fill weight per container		10.6	10.6

- **Description of container closure system** –
  (See Seq 0001, Section 3.2.P.1, *Description and Composition of the Drug Product.pdf*)

  10.6 g of each formulation is filled in a (b) (4) aluminum canister closed with a 50 µL primeless metering valve. The canister is combined with a breath actuated inhaler. The breath actuated inhaler consists of two parts, the Force Holding Unit (FHU) and the Main Body Assembly (MBA). The FHU and MBA are beige for the 40 µg strength and maroon for the 80 µg strength drug product, respectively. Figure 1 was provided in the *Description and Composition of the Drug Product.pdf* (Seq 0001, Section 3.2.P.1) as a schematic showing the proposed container-closure system, which has been reproduced below.

Figure 1: Schematic Showing Sub Assemblies of the BDP BAI Inhaler



Acceptable

Reviewer's Assessment: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2.5 Microbiological Attributes

- **Container/Closure and Package Integrity-** N/A. The drug product is non-sterile.
- **Antimicrobial Effectiveness Testing-**
  (See Seq 0001, Section 3.2.P.2, *DPC-Microbial Challenge-Introduction.pdf*)

  The drug product is multi-dose and the applicant provides a report, entitled *Drug Product Characterization Beclomethasone Dipropionate Nasal Aerosol 80 mcg, 120 Actuations Microbial Challenge* and dated 09 May 2011, for a microbial challenge study for a drug product with the identical formulation as QVAR REDIHALER (Beclomethasone dipropionate), 80 µg. USP<51> was referenced for methods. In addition to the compendial challenge microorganisms, *Bacillus subtilis* was used in the study. Although USP <51> was referenced, the study did not completely follow USP <51>. A lower than recommended inoculum of (b) (4) CFU for each challenge microorganism was used in testing and the positive controls of *S. aureus*, *E. coli*, and *P. aeruginosa* had reduced growth by Day 14. The majority of the challenge microorganisms demonstrated a 3-log

reduction in microbial counts over the 14 day incubation with drug product. Only *B. subtilis* survived in the drug product in low numbers (only demonstrated a (b) (4) reduction).

Acceptable

Reviewer's Assessment: Although this is a multi-dose product, it is a (b) (4) powder formulated with (b) (4) propellant, and thus is non-aqueous. USP <51> Antimicrobial Effectiveness Testing is indicated for multi-dose aqueous-based products. The applicant's study was some type of modification of USP <51>, and the results failed to meet the acceptance criteria of USP <51>. However, the study demonstrated that the formulation did not support and promote growth of the tested microorganisms. The non-aqueous formulation of the subject drug product provides a poor environment to allow potential growth of any bioburden or extrinsic contamination. Also, the drug product is packaged under pressure, which would assist in preventing external contaminants from entering the container and formulation. Therefore, further information will not be requested. (It should also be noted that this same drug product formulation is currently approved in NDA 202813) The multi-dose usage of the drug product poses minimal risk to patient safety from the product quality microbiology perspective.

P.3 Manufacture
P.3.1 Manufacturers

Drug product
IVAX Pharmaceuticals Ireland (aka Teva Pharmaceuticals Ireland)
IDA Industrial Park
Cork Road, Waterford
Ireland

Acceptable

P. 3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

P.3.5 Process Validation and/or Evaluation- N/A

P.5 Control of Drug Product

P.5.1 Specifications (See Seq 0001, Section 3.2.P.5.1- *Specification.pdf*)

The release specification for the drug product includes:

- Total Aerobic Microbial Count with the acceptance criterion of NMT (b) (4) cfu/g
- Total Combined Molds and Yeast Count with the acceptance criterion of NMT (b) (4) cfu/g
- *Staphylococcus aureus* with the acceptance criterion of absent in (b) (4) g
- *Pseudomonas aeruginosa* with the acceptance criterion of absent in (b) (4) g
- Bile tolerant Gram-negative bacteria with the acceptance criterion of absent in (b) (4) g

P.5.2 Analytical Procedures

- **Endotoxin** – N/A
- **Sterility** – N/A
- **Microbial Limits**

The drug product undergoes Microbiological Examination at release according to USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). Verification studies were conducted as described in USP with acceptable results.

Acceptable

Reviewer's Assessment: The applicant has met regulatory expectations with regard to the specification and test method suitability for monitoring the microbial limits of the subject drug product.

P.7 Container Closure System- N/A

P.8 Stability

P.8.1 Stability Summary and Conclusion

(See Seq 0001, Section 3.2.P.8.1, *Stability Summary and Conclusions.pdf*)

An 18-month expiration dating period has been proposed for both the 40µg and the 80µg strength formulations of the subject drug product.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

(See Seq 0001, Section 3.2.P.8.2, *Post-approval Stability Protocol and Stability Commitment.pdf*)

Stability testing will be performed for each strength of the drug product at zero, 3, 6, 9, 12, 18 and 24 months at 25°C ± 2°C/60% ± 5% R.H. as part of the post-approval stability protocol. It is noted that Microbiological Examination testing will be performed on stability; however, the time points for this testing are not listed.

21 February 2017 Information Request: *Section 3.2.P.2.5 Pharmaceutical Development includes the statement that "the finished drug product will be tested for microbial content as per test method Microbiological Examination of Nonsterile Inhalation product as part of release testing and subsequent stability evaluation;" however, there is no such statement in Section 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment. It is unclear if Microbial Examination testing will be performed as part of the post-approval stability protocol. Clarify whether microbiological examination of the product will be performed as part of the post-approval stability protocol. If so, indicate the method and time points for testing.*

Summary of the applicant's response, received 02 March 2017: Microbial Examination testing will be performed as part of the post-approval stability protocol at 0, 6, 12, 18 (if shelf life of the product is 18 months), and 24 months for the first three commercial batches of each strength of the drug product, and annual stability batch of each strength thereafter. The same analytical procedures described in Section 3.2.P.5.2 will be used for testing.

P.8.3 Stability Data

(See Seq 0001, Section 3.2.P.8.3)

Three exhibit batches for the 40 µg (RD #s 1502, 1503 and 1504) and 80 µg strength drug product (RD #s 1505, 1506 and 1507) were tested for microbiological quality at long term conditions (25°C/60% RH at initial, 6 and 12 months), accelerated conditions (40°C/75% RH at initial and 6 months) and intermediate (30°C/65% RH at initial, 6 and 12 months) and were within specification limits.

Acceptable

Reviewer's Assessment: The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life. In addition, the stability data submitted to date support the microbiological quality of the subject drug product.

R Regional Information

Executed Batch Records

Executed batch records were provided for exhibit batch #s RD 1504 and RD 1505 for the 40µg and 80µg strength formulations of the subject drug product.

Acceptable

Reviewer's Assessment: The batch records confirm that the described manufacturing processes were used for the production of the exhibit batches.

Comparability Protocols- N/A.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q)
MODULE 1
2.A. Package Insert-N/A.

Post-Approval Commitments- N/A.

Lifecycle Management Considerations- N/A.

Primary Microbiology Reviewer Name and Date: Daniel J. Schu, Ph.D. (5/15/17)
Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Marla Stevens-Riley, Ph.D.
"I concur." (5/15/17)

Marla
Stevens Riley

Digitally signed by Marla Stevens Riley
Date: 5/15/2017 09:02:45AM
GUID: 508da70c00028f21637ed864c514d12a

Daniel
Schu

Digitally signed by Daniel Schu
Date: 5/15/2017 02:27:44PM
GUID: 55919d6300e16b08a5f33c77046bd421

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 207921	**Submission Type: 505(b)(2)**	**Established/Proper Name: beclomethasone dipropionate**
Applicant: Norton (Waterford) Ltd.	**Letter Date: 01-OCT-2016**	**Dosage Form: inhalation aerosol**
Chemical Type: 5	**Stamp Date: 03-OCT-2016**	**Strength: 40 and 80 mcg/act**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			Describe potential review issues here or on additional sheets

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☐	☒	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☐	☒	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	Proposed for use down to age 4
10.	Locally acting drug[1]	☒	☐	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product _____	☐	☒	Drug and device not regulated separately
19.	Other_____	☒	☐	Drug product is breath-actuated

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Regulatory Considerations				
20.	USAN Name Assigned	☒	☐	
21.	End of Phase II/Pre-NDA Agreements	☒	☐	• 2 week repriming period agreed upon for study • agreed that microbial challenge study not needed • study with spacers at 15 and 30 L/min conducted and warning labeling included in labeling if necessary • applicant will study effects of mouthpiece opening and closing delays (misuse scenarios) • adverse effects of shaking and orientation to be studied • *in vitro* comparability to approved QVAR MDI to be demonstrated (DDU, APSD, spray pattern, plume geometry), but not required • robustness of the valve studied in terms of priming/repriming, temperature cycling, dropping, delay times, orientation • Agency **did not agree** to accept only (b) (4) (b) (4) of stability data for the foreign particulate and leachable parameters (12 months of data necessary) • We agreed to the applicants control strategy for extractables/leachables • We required at least 3 months of accelerated and long term stability for drug product with the (b) (4) device assembly from a second manufacturing site (b) (4) • Agency agreed to allow batch number on actuator only (not on filled canister) • (b) (4) defect discussed in terms of impact on drug product characterization studies (planned repeat of temperature cycling and drop test; see 02-NOV-2015 WRO) • Agency **did not agree** to only (b) (4) of stability data for 60 dose sample product presentation • Antimicrobial effectiveness testing recommended as per USP <51>; microbiology team agreed in principle with the validation of the microbial examination method • (b) (4)
22.	SPOTS (Special Products On-line Tracking System)	☐	☒	
23.	Citizen Petition and/or Controlled Correspondence	☐	☐	Unknown

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

	Linked to the Application			
24.	Comparability Protocol(s)[2]	☐	☒	
25.	Other_____	☒	☐	Applicant claims to be using a "primeless" valve, which may have implications regarding labeling/patient instructions relative to previously approved breath-actuated MDI drug products
	Quality Considerations			
26.	Drug Substance Overage	☒	☐	The applicant uses a (b) (4) overage of the active during manufacturing (b) (4)
27.	Design Space – Formulation	☐	☐	
28.	Design Space – Process	☐	☐	
29.	Design Space – Analytical Methods	☐	☐	
30.	Design Space – Other	☒	☐	(b) (4)
31.	Real Time Release Testing (RTRT)	☐	☒	
32.	Parametric Release in lieu of Sterility Testing	☐	☐	N/A
33.	Alternative Microbiological Test Methods	☐	☐	Microbiology team will address this
34.	Process Analytical Technology[1]	☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications – Drug Product	☒	☐	
36.	Non-compendial Analytical Procedures and/or specifications – Excipients	☒	☐	
37.	Non-compendial Analytical Procedures and/or specifications – Microbial	☐	☐	Microbiology team will address this
38.	Unique analytical methodology[1]	☐	☒	
39.	Excipients of Human or Animal Origin	☐	☒	
40.	Novel Excipients	☐	☒	
41.	Nanomaterials[1]	☐	☒	
42.	Hold Times Exceeding 30 Days	☐	☒	
43.	Genotoxic Impurities or Structural Alerts	☒	☐	(b) (4)
44.	Continuous Manufacturing	☐	☒	
45.	Other unique manufacturing process[1]	☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	☐	☐	
47.	New delivery system or dosage form[1]	☒	☐	The breath-actuated MDI device design is not one that has been approved yet
48.	Novel BE study designs	☐	☐	For clinical pharmacology to address
49.	New product design[1]	☒	☐	See 47 above
50.	Other_____	☐	☐	

[1]Contact Office of Testing and Research for review team considerations

[2]Contact Post Marketing Assessment staff for review team considerations

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Expected (aquatic) Introduction Concentation less than 1 ppb
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols	☐	☒	☐	No comparability protocols are included; no separate method validation package is included (may be relevant if reviewer decides to ask FDA laboratory to assess one or more methods)
	FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☐	☒	☐	Four sites listed on 356h; (b) (4) DMF 4871 not indicated on 356h, but LoA is provided in references section of module 1 fot this API manufacturer; Ivax Ireland telephone facsimile not provided
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
	DRUG SUBSTANCE INFORMATION				

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☒	☐	☐	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment	☐	☐	☐	Most information for the API is provided by reference to (b) (4) DMF 4871, which also supports Teva's approved and currently marketed Qvar Inhalation Aerosol of NDA 20911; thus it is highly likely that the necessary information is available for review via that file
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used	☐	☒	☐	(b) (4)

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				(b) (4)
	BIOPHARMACEUTICS				
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☐	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product?	☐	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)				
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☐	☐	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☐	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☐	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☐	
	REGIONAL INFORMATION AND APPENDICES				
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	☐	☐	☒	
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be	☐	☐	☒	

C. FILING CONSIDERATIONS					
	marketed with summaries of test results for those samples				

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

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW Attachment 2 – Risk Assessment

DP attribute/ CQA	Factors that can impact the CQA[1]	O[2]	S[2,3]	D[2]	FMECA RPN #	Comment & considerations
Delivered Dose Uniformity	(b) (4)	3	3	3	27	(b) (4)

[1] Patient mis-use can impact performance of device but human factors are beyond scope of CMC evaluation

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

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

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW Attachment 2 – Risk Assessment

						(b) (4)

Aerodynamic Particle Size Distribution (APSD)	(b) (4)	3	3	3	27	(b) (4)
Spray Pattern (see (b) (4)		2	3	5	30	

Craig
Bertha

Digitally signed by Craig Bertha
Date: 10/17/2016 08:12:22AM
GUID: 50841a65000098a9383c817879a6a84d