CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208798Orig1s000

CHEMISTRY REVIEW(S)


NDA-208798-ORIG-1 Manufacturing Facility Inspection
Overall Manufacturing Inspection Recommendation
Edit Task
Task Actions
Task Summary
Task Details
Documents
Approvals
Updates
Application Life Cycle
Inspection Management Form
Assigned To
Christina Capacci-Daniel
Edit Assignment
This was done on
Nov 30, 2016
Status
Complete
This task is waiting on
Facilities
Last Update
Dec 1, 2016
Submitted On
Mar 29, 2016
Reference Number
7216630
Inspection Management Form
As of Jan 27, 2017 11:23 am GMT
NDA-208798-ORIG-1
(b) (4)
TEVA PHARMACEUTICALS IRELAND (DBA IVAX PHARMACEUTICALS IRELAND) | 3002807777 | ADM AEROSOL DISPERSED MEDICATION | Approve Facility
TEVA PHARMACEUTICALS IRELAND (DBA IVAX PHARMACEUTICALS IRELAND) | 3002807777 | ORD ORALLY INHALED DELIVERY | Approve Facility
TEVA PHARMACEUTICAL INDUSTRIES LIMITED | 3002874027 | NEC NOT ELSEWHERE CLASSIFIED | Approve Facility
TEVA PHARMACEUTICAL INDUSTRIES LIMITED | 3005202697 | CTL CONTROL TESTING LABORATORY |
Overall Manufacturing Inspection Recommendation
Approve
Withhold
Cancel
Submission Manufacturing Facilities
Facility Status
Completion Date
Project Area
FEI
DUNS
Facility ID
Facility Name
Approve Facility 11/29/2016 NDA-208798-ORIG-1 3002807777 985123517 110005042 TEVA PHARMACEUTICALS IRELAND
Approve Facility 11/29/2016 NDA-208798-ORIG-1 3002874027 600029549 110018913 TEVA PHARMACEUTICAL INDUSTRIE
Approve Facility (b) (4) NDA-208798-ORIG-1 (b) (4) (b) (4)
No Further Evaluation NDA-208798-ORIG-1
Approve Facility 5/4/2016 NDA-208798-ORIG-1 3002807777 985123517 110005042 TEVA PHARMACEUTICALS IRELAND

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)

Date:	September 26, 2016 **(Updated 11/1/2016)**
To:	Art Shaw, CDER, OPQ, ONDP, Arthur.Shaw@fda.hhs.gov
CC:	Office of Combination Product at: combination@fda.gov Regulatory Business Program Manager (RBPM)/Regulatory Program Manager (RPM): Florence Aisida E-Mail: Bamidele.Aisida@fda.hhs.gov CDER/OPQ/OPF: Juandria.Williams@fda.hhs.gov
Through:	Francisco Vicenty, REGO/DMQ/OC, CDRH, WO 66, Rm 3426, E-mail: Francisco.Vicenty@fda.hhs.gov Rakhi Dalal, REGO/DMQ/OC, CDRH, WO 66, Rm 3454, E-mail: Rakhi.Dalal@fda.hhs.gov Rakhi M. Panguluri -S Dig tally signed by Rakhi M Panguluri S DN: c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 130020021 0 cn Rakhi M Panguluri S Date: 2016 12 01 08:35:30 05 00
From:	Crystal Lewis, REGO/DMQ/OC, CDRH, WO 66, Rm 3452, E-mail: Crystal.lewis@fda.hhs.gov
Applicant/Licensure:	Teva Pharmaceutical Industries Ltd. 5 Basel Street Petach Tikva, Israel 4951033 FEI: 3002874027
Submission (Type & Number):	NDA 208798
Combination Product Name:	Fluticasone propionate
Combination Product Intended Use:	Product is intended for the treatment of asthma as a prophylactic therapy.
Device Constituent (Type):	Multidose Dry Powder Inhaler (MDPI)
ICCR Number:	ICC1600240
ICCR Instruction (ICCR Form):	Consultative Review
Pre-Approval Facility Inspection:	No See Inspection Guidance, ICCR Memo date, Page #14
Documentation Review	**Complete**
CDRH/OC Recommendation:	**Approvable**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of Fluticasone propionate, NDA 208798.

PRODUCT DESCRIPTION

Fluticasone propionate is the active pharmaceutical ingredient of the multidose dry powder inhaler (Fp MDPI). The MDPI is the primary container closure system and consists of an inspiratory flow driven device that contains a reservoir. Together, fluticasone proprionate and the MDPI form the combination product (CP). The CP is utilized for the treatment of asthma as prophylactic therapy. The Fp MDPI is provided in three strengths 55mcg, 113mcg, and 232mcg. Each strength of the Fp MDPI delivers 60 actuations and one actuation represents one therapeutic dose of the drug product, see figure 1 below.

The Fp MDPI device consists of (b) (4) The firm provides a description and illustration for the device (b) (4) functions. These documents are found in section 3.2.P.2.4 Container Closure System. Figure 1 provides an illustration of the Fp MDPI device indicating (b) (4).

Figure 1: Functional Representation of the Fp MDPI Device

(b) (4)

REGULATORY HISTORY

The following facility was identified as being subject to applicable Quality System Requirements under 21 CFR part 820 and 21CFR Part 4.4:

1. Teva Pharmaceutical Industries Ltd.
   5 Basel Street
   Petach Tikva, Israel
   4951033
   FEI: 3002874027

Responsibility – This manufacturer is the NDA 208798 holder and applicant and should conform to 21 CFR Part 4 for the finished combination product. This is also the correspondence address for the firm. No inspectional history is available for the applicant at FEI# 3002874027. CDRH/OC recommends a post-approval inspection of the applicant at FEI 3002874027.

Inspection Recommendation:
An inspection is not required because:

- No manufacturing activity for the combination product occurs at this site.

2. IVAX Pharmaceuticals (aka Teva Pharmaceuticals Ireland)
   Unit 301 Industrial Park, Cork Road
   Waterford, Ireland 999999
   FEI # 3002807777

Responsibility – This manufacturer is responsible for the testing and release of raw materials, device and packaging components. This facility also performs manufacturing, packaging and in-process testing of the finished product. Testing and release of finished product, stability testing of finished product and batch release also occurs at this facility.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed an inspection was performed September 7- September 10, 2015. The inspection covered drugs and was classified NAI.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product. Therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance, p. 12).

Inspection Recommendation:
An inspection is not required because:

- A recent medical device inspection of the firm was acceptable.

DOCUMENTATION REVIEW
The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20
(Updated 11/1/16)
The firm has identified Teva Pharmaceuticals Ireland (TPI) as the site with the ultimate responsibility for the overall combination product. Teva's Quality Policy Document defines the firm's management control procedures and describes the Pharmaceutical Quality System. The roles, responsibilities, and authorities of the Quality System for the entire organization are defined in the Quality Policy document. Additional documents included in TPI's management controls include: Responsibilities of the Quality Unit Charter, Quality Council, Compiling and Reviewing Annual Product Reviews, Annual Reports and Product Quality Reviews. See figure 2 for a high level organizational structure of the firm's quality management.

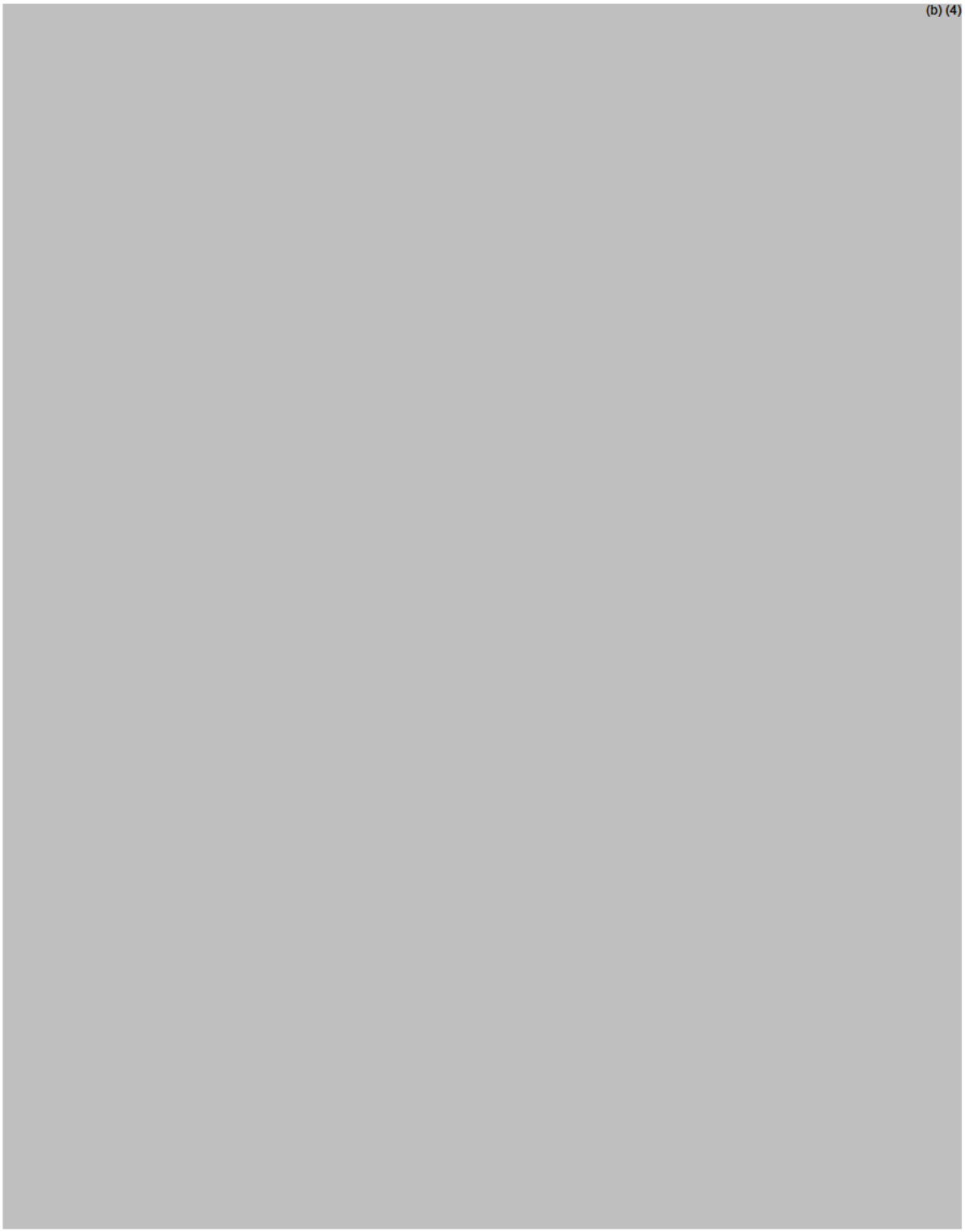
The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Figure 2. TPI High Level Organizational Structure of Quality Management

Design Control, General, 21 CFR 820.30
(Updated 11/1/16)

The MDPI or primary container closure system's design is formulated on a patented pneumatic system. This pneumatic system is utilized in metering the drug contained in the powder blend from the reservoir. A fixed volume dose cup transfers the metered dose to an inhalation position thereby making it available for inhalation. The inhalation pathway is separated from the bulk blend and only the metered dose is made available for inhalation. Once available, the metered dose becomes aerosolized and ready for delivery from the device. The device is also designed to prevent overdosing following multiple actuations before inhalation.

Further, the firm describes the design and development of the device being the responsibility of



The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100
(Updated 11/1/16)

TPI's CAPA system includes investigating, understanding, and correcting discrepancies as well as

preventing their recurrence. A systemic approach is utilized to identify necessary corrective and preventive actions and evaluate their effectiveness. (b) (4)

(b) (4)

(b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR820.100.

Installation, 21 CFR 820.170

Installation is not required for this combination product.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product.

MANUFACTURING

Production and Process Controls

TPI provided documentation for its manufacturing process for the fluticasone propionate inhalation powder product and metered dose inhalation products (MDIP). MDPI products are

manufactured under the RespiClick brand name in the United States but were originally identified as Spiromax outside the US. This product is a non-sterile inhalation product contingent on microbiological examination testing per USP<1111>/Ph.Eur 5.1.4/JP 4.05. Routine microbial controls are performed including TPI's microbiology environmental policy (EMP) to ensure satisfactory microbiological control for the combination product. EMP covers overall quality, safety and efficacy for (b) (4) manufacture for the finished product.

The RespiClick device is a Multi-dose Dry Powder Inhaler (MDPI) device and dispenses a metered dose of fluticasone propionate and is administered through the patient's inspiration. The MDPI device is comprised of (b) (4)

(b) (4)

(b) (4)

Production Flow

The firm provided a process flow chart detailing an overview of the steps for the Fp MDPI manufacturing process, see figure 5 Flowchart of Fp MDPI Manufacturing Process below.

Figure 5: Flowchart of Fp MDPI Manufacturing Process

Acceptance Activities

The firm provided acceptance criteria documentation in section 2.3.P.5.1 An overview of the firm's release and stability specifications for Fluticasone Proprionate inhalation powder 55,113 and 232 mcg, 60 actuation products are described in table 13, see below. Table 13 also details individual tests utilized for the device's acceptance criteria.

Table 13: Release and Stability Specifications for Fluticasone Propionate Inhalation Powder 55, 113 and 232 mcg, 60 Actuations products

Test	Acceptance Criteria
Appearance:	
Appearance of Inhaler	An inhaler with a (b) (4) green mouthpiece cover (complies with standard). Absence of visual damage or powder leakage. The numeral 60 is visible in the dose counter window.
Appearance of Powder by Visual Inspection	White (b) (4) powder.
Appearance of Powder by UV-Vis	Reflectance ≥ (b) (4) %
Identification by UPLC[a]	Retention time of principle peak in the sample is within (b) (4) % of the corresponding retention time of fluticasone propionate peak in the standard.
Identification by TLC[a]	The retention factor (R_F) of the principle spot in the sample must correspond to that obtained for the fluticasone propionate standard.
Determination of Assay (Drug Content) by UPLC: 55 mcg 113 mcg 232 mcg	 (b) (4) %w/w %w/w %w/w
Determination of Related Substances and Degradation Products	Any Individual Unspecified Impurity (Unknown) NMT (b) (4) % Total Impurities NMT %
(b) (4)	
Net Content (Fill Weight)[a]	(b) (4) g

Table 13: Release and Stability Specifications for Fluticasone Propionate Inhalation Powder 55, 113 and 232 mcg, 60 Actuations products (Continued)

Test	Acceptance Criteria
Dose Content Uniformity (DCU)	The Label Claim Emitted Dose (LCED) for fluticasone propionate is 51mcg. (b) (4)

Table 13: Release and Stability Specifications for Fluticasone Propionate Inhalation Powder 55, 113 and 232 mcg, 60 Actuations products (Continued)

Test	Acceptance Criteria
Dose Content Uniformity Through Inhaler Life (DCU TL)	The LCED for fluticasone propionate is 51 mcg. (b) (4)
Number of Actuations per Inhaler	NLT 60 actuations
Dose Counter Reading	After (b) (4) actuations: (b) (4)

Table 13: Release and Stability Specifications for Fluticasone Propionate Inhalation Powder 55, 113 and 232 mcg, 60 Actuations products (Continued)

Test	Acceptance Criteria	
Aerodynamic Particle Size Distribution (APSD) by (b) (4)		
55 mcg	(b) (4)	(b) (4)
113 mcg		(b) (4)
232 mcg		
Device Flow Resistance	(b) (4)	$(kPa^{0.5})/(L/min.)$
Foreign Particulate Matter	≥ 2 µm and < 10 µm ≥ 10 µm and < 25 µm ≥ 25 µm	(b) (4)
Microbiological Examination of Nonsterile Inhalation Products	Total Aerobic Microbial Count (TAMC):	NMT (b) (4) CFU/g
	Total Combined Yeasts and Moulds Count (TYMC):	NMT (b) (4) CFU/g
	Bile-tolerant Gram-negative Bacteria:	Absent/g
	Pseudomonas aeruginosa:	Absent/g
	Staphylococcus aureus:	Absent/g

[a] For release only

Documentation Review Recommendation

The application for Fluticasone propionate, NDA 208798 is approvable from the perspective of the applicable Quality System Requirements.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

CDRH/OC RECOMMENDATION

(1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

(2) There were no facility inspections for compliance with applicable Quality System Requirements needed for approvability determination.

Crystal Lewis -S

Digitally signed by Crystal Lewis -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Crystal Lewis -S, 0.9.2342.19200300.100.1.1=2000430186
Date: 2016.12.01 09:23:13 -05'00'

Crystal Lewis

Prepared: Clewis: 9/26/16, 11/1/16, 11/10/16, 11/16/16
Reviewed: RDalal: 9/27/2016, 10/5/2016, 12/01/2016

CTS No.: ICC1600240
NDA 208798

Review Cycle Meeting Attendance:
None

Inspectional Guidance
Firm to be inspected:
1. IVAX Pharmaceuticals (aka Teva Pharmaceuticals Ireland)
Unit 301 Industrial Park, Cork Road
Waterford, Ireland 999999
FEI # 3002807777

CDRH recommends that during the next inspection of Teva Pharmaceuticals Ireland, Waterford, Ireland (FEI #3002807777), a comprehensive baseline inspection focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) be considered. Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY
The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related. Questions regarding this consult should be referred to one of the following individuals:

Primary Contact
Crystal Lewis
CSO,
REGO,
DMQ
Office of Compliance, WO66 RM 3452
Phone: 301-796-6116

Secondary Contacts (if Primary is unavailable and a timely answer is required)
Francisco Vicenty
Branch Chief,
REGO,
DMQ
Office of Compliance, WO66 RM 3426
Phone: 301-796- 5577

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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

/s/

STEVEN A KINSLEY
01/19/2017
This review is a revision of review entered into DARRTS on 10/21.

Recommendation: Approval

NDA 208798
Review #1

Drug Name/Dosage Form	Fluticasone propionate (ArmonAir™ RespiClick®) inhalation powder
Strength	55, 113, 232 mcg metered/actuation
Route of Administration	Oral inhalation
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceutical Industries Ltd.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*28-MAR-2016*	
Amendment	*03-JUN-2016*	*Drug product, process*
Amendment	*01-JUL-2016*	*Drug product*
Amendment	*14-JUL-2016*	*Drug product*
Amendment	*16-SEP-2016*	*Drug product, process*
Amendment	*07-OCT-2016*	*Drug product*
Amendment	*20-OCT-2016*	*CDRH OC*
Amendment	*28-OCT-2016*	*Process*
Amendment	*10-NOV-2016*	*Drug product*
Amendment	*17-NOV-2016*	*Drug product*
Amendment	*18-NOV-2016*	*Drug product*
Amendment	*01-DEC-2016*	*Drug Product*
Amendment	*09-DEC-2016*	*Drug Product*
Amendment	*12/DEC-2016*	*Drug Product*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Benjamin Stevens	II/Division of New Drug API
Drug Product	Arthur Shaw	IV/DNDPII
Process	Joanne Wang	IV/DPAII
Microbiology	Joanne Wang	IV/DPAII
Facility	Christina Capacci-Daniel Crystal Lewis (CDRH OC)	II/DIA REGO/SMQ/OC, CDRH
Biopharmaceutics	N/A	
Regulatory Business	Florence Aisida/Steve	I/Division I

Process Manager	Kinsley	
Application Technical Lead	Craig M. Bertha	IV/DNDPII
Laboratory (OTR)	N/A	
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
15745	II	Teva Pharmaceuticals Industries Ltd.	Fluticasone propionate	Adequate	08-SEP-2016	
(b) (4)	IV		(b) (4)	Adequate	31-OCT-2016	
	III			Adequate	31-OCT-2016	
	III			Adequate	07-JUN-2016	
	III			Adequate	31-OCT-2016	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	108838	Teva's IND for the fluticasone propionate inhalation powder
NDA	208799	Teva's NDA for the fluticasone propionate/salmeterol xinafoate inhalation powder using the same device

2. CONSULTS

DISCIPLINE	STATUS	RECOMMEN-DATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH OC	Final	Approval	1-NOV-2016	Crystal Lewis
Clinical				
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the reviews and recommendations from the drug substance, drug product, process, and facilities teams outlined in the review below, an overall recommendation of **approval** is forwarded to the clinical Division (DPARP).

The approved expiration dating periods for the three strengths of the drug product, 55, 113, and 232 mcg metered per actuation, are 12, 13 and 17 months, respectively.

II. Summary of Quality Assessments

A. Product Overview

The Agency approved Teva's ProAir® RespiClick® (albuterol) inhalation powder drug product (NDA 205636) that used a version of the RespiClick® device that is used for this application (note that there are some minor differences). The current fluticasone propionate (FP) inhalation powder drug product is proposed to be used to treat asthma. The drug product is proposed with three strengths (55, 113, and 232 mcg/metered actuation).

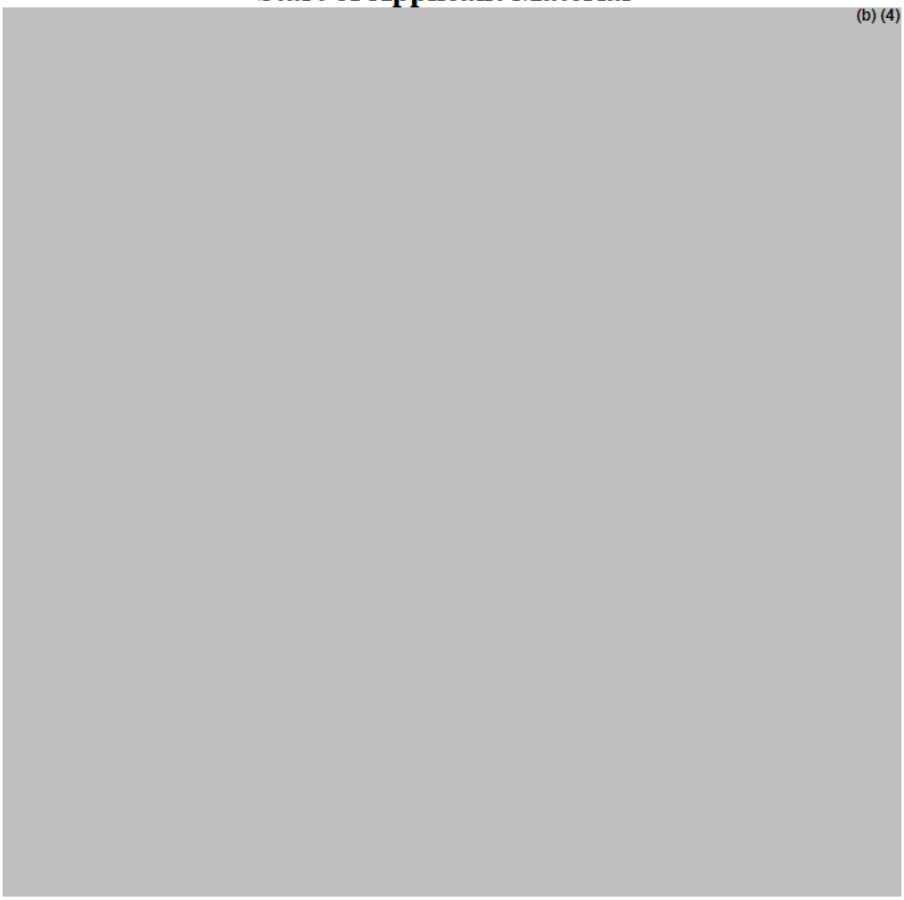
Proposed Indication(s) including Intended Patient Population	Treatment of asthma in patients 12 years and above
Duration of Treatment	Chronic
Maximum Daily Dose	464 mcg/day
Alternative Methods of Administration	Fluticasone propionate is also available for topical and nasal application

B. Quality Assessment Overview

The application is submitted in support of a fluticasone propionate (ArmonAir™ RespiClick®) inhalation powder drug product for the treatment of asthma. There have been previous FP inhalation powder drug products approved, most notably, the Flovent Diskus from GSK. The current device for this combination product is a reservoir type (device-metered) of inhalation product, as compared to the GSK Diskus drug product, which is a pre-metered inhalation powder drug product. The formulations in the reservoirs for each strength are composed (b) (4) lactose monohydrate, with (b) (4) w/w of (b) (4) FP for the 55, 113, and 232 mcg strengths,

respectively. A schematic drawing of the device is reproduced below from the application:

Start of Applicant Material



End of Applicant Material

In summary, the patient opens the mouthpiece cover, which results in the metering of a dose by movement of the formulation-filled dose cup into the position necessary for inhalation. Upon inhalation through the mouthpiece, the airflow draws the metered dose from the dosing cup, the cyclone (b) (4) helps deagglomerate the FP (b) (4), and the dose then exits the mouthpiece to be inhaled by the patient. The closure of the mouthpiece cover resets the dosing cup (b) (4), and the counter counts down by one unit. The drug product includes protective package (aluminum laminate pouch with enclosed silica gel desiccant) which is removed by the patient before first use. Each strength drug product delivers 60 actuations, which is sufficient for 30 days of dosing. This in-use period is supported by the stability data provided in the application with protective packaging removed. Each strength of the drug product currently is granted the following expiry periods:

Strength (µg)	Expiration Date (month)
55	12
113	13
232	17

These periods were mainly limited by the end-of-unit life dose content uniformity testing results, which trended lower with time. While it is not ideal to have different expiration dating periods for each strength, these were supported by the data, and it may be that as more stability data are attained, the applicant will be able to extend these and perhaps propose a single expiry period for all strengths.

The majority of the information supporting the drug substance was included in DMF 15745 (refer to the review of this file for more details). FP is a corticosteroid commonly used for its anti-inflammatory effect for the treatment of asthma. The drug is compliant with the USP monograph standard but with additional requirements applied for appearance, particle size, heavy metal impurities, inorganic impurities, residual solvents, and microbiological characteristics. The retest period established is (b) (4) years.

It is notable from the drug product portion of the review, that there have been some changes to the device as the development has proceeded (e.g., the version of the RespiClick device used here includes (b) (4) However, these changes either took place early in development or are supported with comparative data to provide assurance that critical device functionality is attained. The applicant presented data from comprehensive characterization studies, as recommended by the Agency for inhalation powder drug products, and these are supportive of the labeling and patient instructions for use as proposed.

From the process perspective, the manufacturing for this combination product involves four main unit operations: (b) (4) . The commercial process and manufacturing site are the same as the site used for production of the registration (b) (4) . Nevertheless, the critical process parameters proposed for commercial batches were supported by registration batch data, the in-process controls are adequate, and acceptance criteria well justified. In addition, the process description provides clear instructions for manufacturing.

The facilities have been assessed and it has been determined that there are no significant, outstanding manufacturing or facility risks that would prevent the approval of the application.

C. Special Product Quality Labeling Recommendations (NDA only): N/A

D. Final Risk Assessment (see Attachment)

APPEARS THIS WAY ON ORIGINAL

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

(b) (4)

ACCEPTABLE

ACCEPTABLE

Reviewer's Assessment: ACCEPTABLE

1

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

3 DOSAGE FORMS AND STRENGTHS

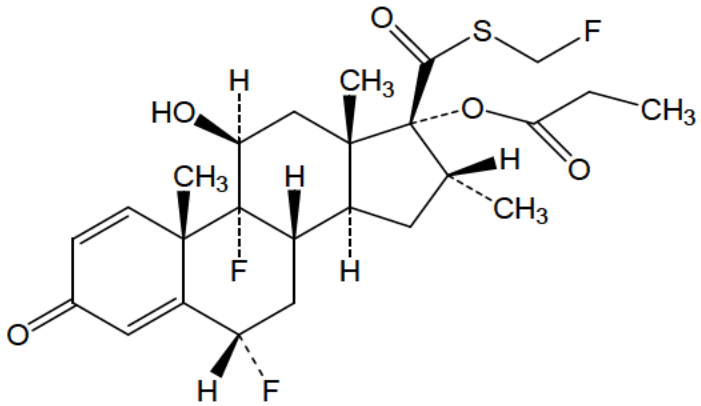
"Inhalation Powder. FP TRADENAME is a multidose, inhalation-driven, dry powder inhaler for oral inhalation that meters 55, 113, or 232 mcg of fluticasone propionate from the device reservoir and delivers 51, 103, or 210 mcg of fluticasone propionate, respectively, from the mouthpiece per actuation. Each inhaler is supplied for 60 actuations. FP TRADENAME is supplied as a white dry powder inhaler with a green cap in a sealed foil pouch with desiccant."

ACCEPTABLE

11 DESCRIPTION

"*The active component of FP TRADENAME 55 mcg, FP TRADENAME 113 mcg, and FP TRADENAME 232 mcg is fluticasone propionate, a corticosteroid having the*

chemical name S-(fluoromethyl) 6α,9-difluoro-11ß,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17ß-carbothioate, 17-propionate, and the following chemical structure:



Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FP TRADENAME is a multidose dry powder inhaler for oral inhalation only. It contains a formulation blend of fluticasone propionate and alpha lactose monohydrate (which may contain milk proteins). The opening of the mouthpiece cover meters 11.5 mg of the formulation from the device reservoir, which contains 55, 113, or 232 mcg of fluticasone propionate. Patient inhalation through the mouthpiece causes the deagglomeration and aerosolization of the drug particles as the formulation moves through the cyclone component of the device. This is followed by dispersion into the airstream.

Under standardized in vitro test conditions, the FP TRADENAME inhaler delivers 51, 103, or 210 mcg of fluticasone propionate with lactose from the mouthpiece.

The amount of drug delivered to the lung will depend on patient factors such as inspiratory flow profiles. In adult subjects (N=50, aged 18 to 45 years) with asthma, mean peak inspiratory flow (PIF) through the FP TRADENAME inhaler was 108.28 L/min (range: 70.37 to 129.24 L/min). In adolescent subjects (N=50, aged 12 to 17 years) with asthma, mean peak inspiratory flow (PIF) through the FS TRADENAME inhaler was 106.72 L/min (range: 73.64 to 125.51 L/min)."

ACCEPTABLE

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

"FP TRADENAME is supplied in the following three strengths as a white dry-powder inhaler. Each inhaler has a green cap and is packaged individually in a foil pouch in a carton. Each inhaler contains 0.9g of the formulation and provides 60 actuations:

STRENGTH	*NDC CODE*
FP TRADENAME 55 mcg	*NDC 59310-705-06*
FP TRADENAME 113 mcg	*NDC 59310-711-06*
FP TRADENAME 232 mcg	*NDC 59310-722-06*

Each FP TRADENAME inhaler has a dose counter attached to the actuator. Patients should never try to alter the numbers for the dose counter. Discard the inhaler when the counter displays 0, 30 days after opening the foil pouch or after the expiration date on the product, whichever comes first. The labeled amount of medication in each actuation cannot be assured after the counter displays 0, even though the inhaler is not completely empty and will continue to operate [see Patient Counseling Information (17)].”

Reviewer’s Assessment: ACCEPTABLE

16.2 Storage and Handling

“Store at room temperature (between 15° and 25°C; 59° and 77°F) in a dry place; excursions permitted from 59°F to 86°F (15°C to 30°C). Avoid exposure to extreme heat, cold, or humidity.

Keep out of reach of children.

FP TRADENAME should be stored inside the unopened moisture-protective foil pouch and only removed from the pouch immediately before initial use. Discard FP TRADENAME 30 days after opening the foil pouch or when the counter reads “0”, whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart.”

Reviewer’s Assessment: ACCEPTABLE

17 PATIENT COUNSELING INFORMATION

The parts of this section that are relevant to CMC are the following:

“Caring for and Storing the Inhaler

***Instruct patients to not open their inhaler unless they are taking a dose**. Repeated opening and closing the cover without taking medication will waste medication and may damage the inhaler.*

*Advise patients to keep their inhaler dry and clean at all times. **Never wash or put any part of the inhaler in water**. Patient should replace inhaler if washed or placed in water.*

Advise patients to immediately replace inhaler if mouthpiece cover is damaged or broken.

Gently wipe the mouthpiece with a dry cloth or tissue once a week.

Instruct patients to store the inhaler at room temperature and to avoid exposure to extreme heat, cold, or humidity.

Instruct patients to never take the inhaler apart.

Inform patients that FP TRADENAME has a dose counter attached to the actuator. When the patient receives the inhaler, the number 60 will be displayed. The dose counter will count down each time the mouthpiece cap is opened and closed. The dose-counter window displays the number of actuations left in the inhaler in units of two (e.g., 60, 58, 56, etc.). When the counter displays 20, the color of the numbers will change to red to remind the patient to contact their pharmacist for a refill of medication or consult their physician for a prescription refill. When the dose counter reaches 0, the background will change to solid red. Inform patients to discard FP TRADENAME when the dose counter displays 0, 30 days after opening the foil pouch or after the expiration date on the product, whichever comes first.

ACCEPTABLE

PATIENT INFORMATION

The parts of this document that are relevant to CMC are the following:

"How should I store FP TRADENAME?

- *Store FP TRADENAME at room temperature between 59°F and 77°F (15°C and 25°C). Avoid exposure to extreme heat, cold, or humidity.*
- *Store FP TRADENAME in the unopened foil pouch and only open when ready for use.*

ACCEPTABLE

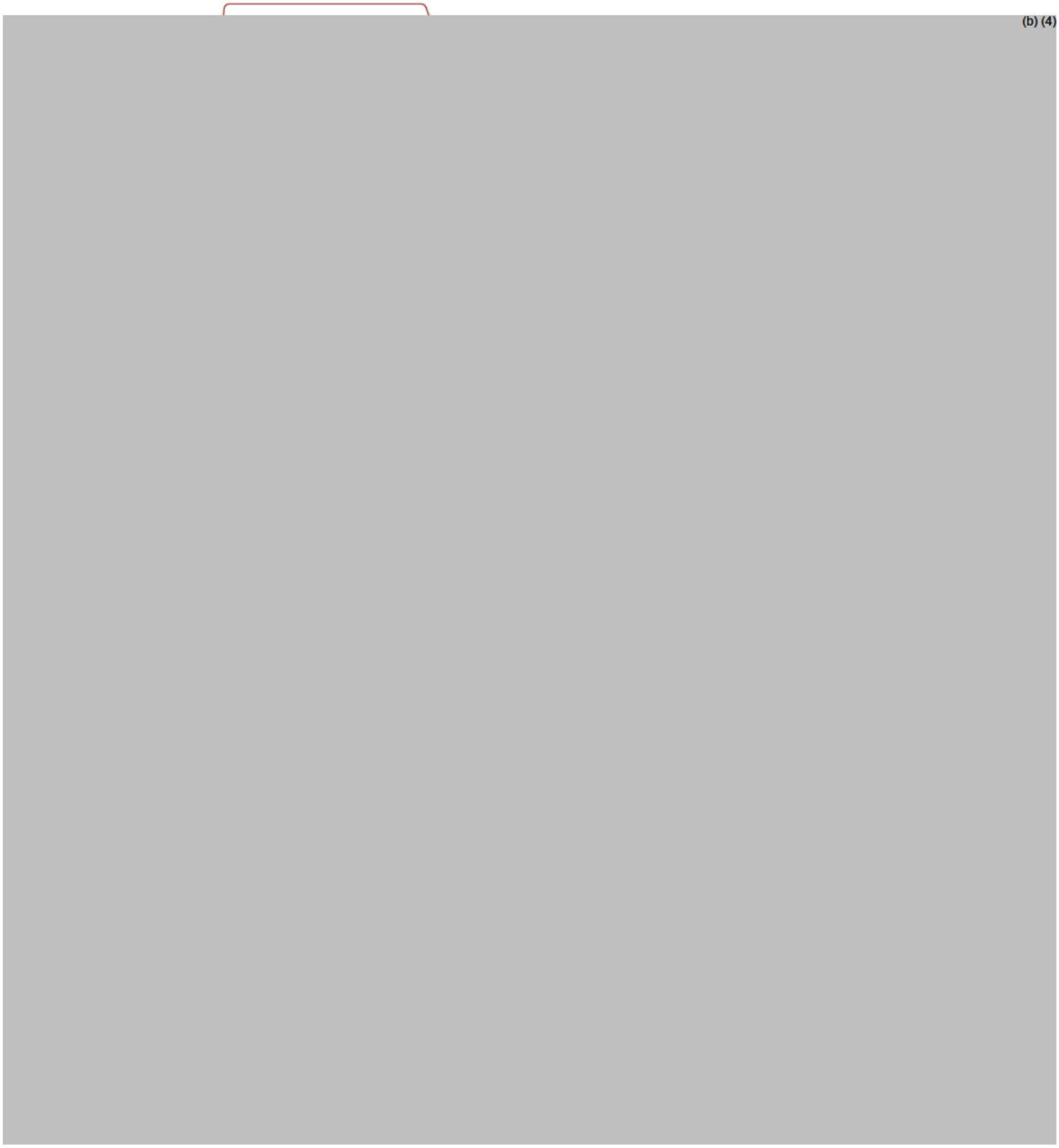
QUALITY ASSESSMENT

Carton Label

Note that the different strengths have the same green color, as do the mouthpiece cover.

Example

(b) (4)



(b) (4)

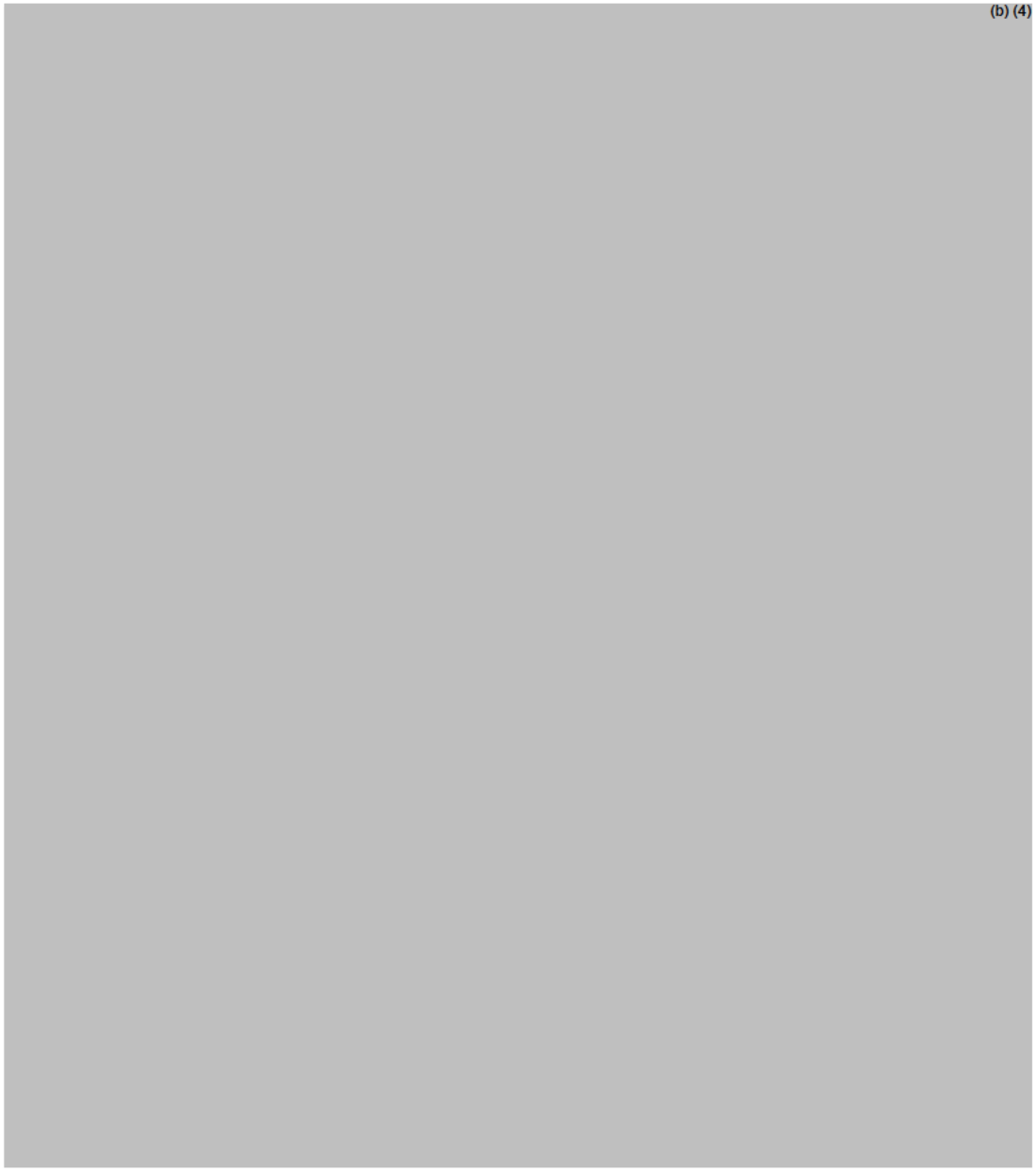
[redacted]

Since the different strengths include the strength in large bold letters, the sameness of the colors is **ACCEPTABLE**

Device Label

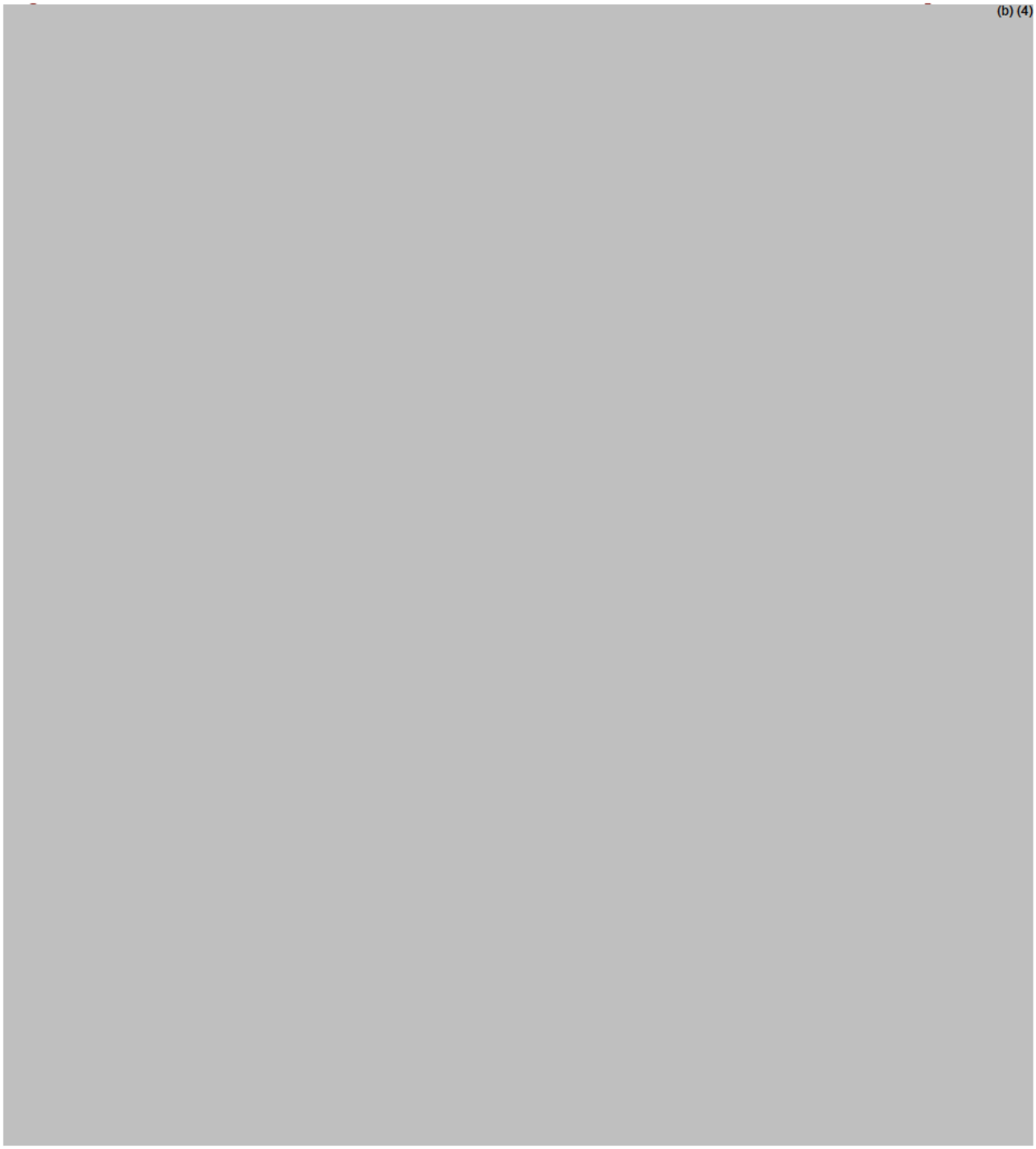
This is particularly important because this is what the patient will see while the opened package is sitting around

Front



Back

(b) (4)



The device label has no information about discarding the device as specified in the Patient's instructions

"Discard FP TRADENAME when the dose counter displays 0, 30 days after opening the foil pouch or after the expiration date on the product, whichever comes first."

There may not be room on the label to include this information. This will be discussed with the team in terms of whether the Patient's Instructions are sufficient.

COMMENT: The device labeling should be evaluated in terms of whether it needs the storage language in the Patient's Instructions:

"Discard FP TRADENAME when the dose counter displays 0, 30 days after opening the foil pouch or after the expiration date on the product, whichever comes first."

Reviewer's Assessment:
ACCEPTABLE

Post-Approval Commitments:
Reviewer's Assessment: None

Lifecycle Management Considerations
Reviewer's Assessment: None

List of Deficiencies: None

QUALITY ASSESSMENT

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	

B. Final Risk Assessment – ANDA

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #	Comments*

ATTACHMENT II: List of Deficiencies for Complete Response

A. Drug Substance Deficiencies

B. Drug Product Deficiencies

C. Environmental Analysis Deficiencies

D. Labeling Deficiencies

E. Process Deficiencies

F. Facilities Deficiencies

G. Biopharmaceutics Deficiencies

H. Microbiology Deficiencies

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name and Date:

1 Document History

Document History	
Author: Integrated Quality Assessment Team, and Don Henry.	

QUALITY ASSESSMENT

Clearance Statement: This document is sponsored by the Integrated Quality Assessment Team. Jorge Rondon (OPRO/OE), Don Henry (OPRP/OE), and the Integrated Quality Assessment Team have cleared this template for use.	This process (CDER OPQ Integrated Quality Assessment Template) will be reviewed at the following intervals and changes to the work aid will be captured as needed: **This process will be reviewed approximately 150 days from date issued (February 18, 2016).**

Version	Summary of Changes	Date Issued
03	Content update	02/18/2016

Julia Pinto

Digitally signed by Julia Pinto
Date: 11/22/2016 12:06 26PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

Arthur Shaw

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Date: 11/22/2016 10:30 32AM
GUID: 508da71e00029e07eb18aead84d4636d

PROCESS

NDA: 208798

Drug Product Name / Strength: ArmonAir RespiClick, Fluticasone Propionate, 55 mcg, 113 mcg, 232 mcg Inhalation Powder

Route of Administration: Oral Inhalation

Applicant Name: Teva Pharmacerutical Industries Ltd.

Review Summary:

The application is recommended for APPROVAL from a process perspective. This is a drug-device combination product. The manufacturing process involves four main unit operations: (b) (4)

Critical process parameters proposed for commercial batches were supported by registration batch data. The in-process controls are adequate and acceptance criteria well justified. The process description provides clear instructions for manufacturing

List Submissions being reviewed (table):

Document(s) Reviewed	Date Received
NDA Original Application	03/29/2016
Response to FDA Request for Information – CMC (13Oct2016)	10/28/2016

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

P.3 Manufacture

Batch Formula

(b) (4)

Table 1: Batch Formulae of Fluticasone Propionate Inhalation Powder 55, 113, and 232 mcg, 60-Actuation Products for a Batch Size of Approximately (b) (4) Inhalers

Ingredient	Quality Standard	Quantity (g)		
		55 mcg	113 mcg	232 mcg
Fluticasone propionate, (b) (4) (g)	USP	(b) (4)		
Lactose monohydrate (g)	USP/NF			
Total (g)				

Batch numbers for the registration batches is provided in 3.2.P.5.4:

Table 1: Phase 3 Clinical and Registration Stability Batches of Fp MDPI Finished Product

Product strength	Batch number	Use of Batch	Certificate of Analysis	CoA Reference
55 mcg	RD1318[a]	Clinical	COA - Finished Product Fp MDPI 55 (Lot RD1318)	QDP0093834
	RD1404	Clinical and Registration stability	COA - Finished Product Fp MDPI 55 (Lot RD1404)	QDP0093835
	RD1407	Registration stability	COA - Finished Product Fp MDPI 55 (Lot RD1407)	QDP0093836
	RD1412	Registration stability	COA - Finished Product Fp MDPI 55 (Lot RD1412)	QDP0093837
113 mcg	RD1315[a]	Clinical	COA - Finished Product Fp MDPI 113 (Lot RD1315)	QDP0093838
	RD1405	Clinical and Registration stability	COA - Finished Product Fp MDPI 113 (Lot RD1405)	QDP0093846
	RD1408	Registration stability	COA - Finished Product Fp MDPI 113 (Lot RD1408)	QDP0093841
	RD1413	Registration stability	COA - Finished Product Fp MDPI 113 (Lot RD1413)	QDP0093844
232 mcg	RD1316[a]	Clinical	COA - Finished Product Fp MDPI 232 (Lot RD1316)	QDP0093845
	RD1406	Clinical and Registration stability	COA - Finished Product Fp MDPI 232 (Lot RD1406)	QDP0093840
	RD1409	Clinical and Registration stability	COA - Finished Product Fp MDPI 232 (Lot RD1409)	QDP0093847
	RD1414	Registration stability	COA - Finished Product Fp MDPI 232 (Lot RD1414)	QDP0093848

[a] Batches manufactured for use in the Phase 3 clinical program only.

Note: Executed Batch Records RD1412, RD1413, RD1414 are provided in 3.2.R

Reviewer's Assessment: Satisfactory

All commercial batch formulas are supported by the corresponding registration batches based on the review of the executed batch records provided in 3.2.R. The commercial batch formulas reflect the proposed product compositions in 3.2.P.1 and the master production records proposed in 3.2.P.3.3. No overage is included.

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Brian Rogers

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Date: 12/16/2016 11:02:12AM
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Joanne Wang

Digitally signed by Joanne Wang
Date: 12/15/2016 04:11 07PM
GUID: 552bcbdd00860c253345cce8856de307

Christina Capacci-Daniel, PhD – December 01, 2016
Acting QAL / Consumer Safety Officer, OPQ/OPF/DIA/IABII

Secondary Reviewer Name and Date:

Derek S. Smith, PhD – December 5, 2016

Derek Smith

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Date: 12/05/2016 04:45 08PM
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Christina Capacci-Daniel

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Date: 12/05/2016 04:44:42PM
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Final Drug Product Risk Assessment - Attachment

DP attribute/ CQA	Factors that can impact the CQA[1]	O[2]	S[2, 3]	D[2]	FMECA RPN #	Comment & considerations
Delivered Dose Uniformity (DDU)	• Inhomogeneity or low formulation assay of FP/lactose blend (e.g., from manufacturing; result of shipping) • Lower than target fill of reservoir • Failure of protective packaging (moisture ingress) • Device malfunction • Amorphous content of FP • Particle size/amorphous content of lactose • Static charge of formulation from manufacturing • Bridging of formulation particles (i.e., crystallization of amorphous material)	2	3	4	24	(b) (4)
Aerodynamic Particle Size Distribution (APSD)	• Inhomogeneity or low assay of FP/lactose blend • Lower than target fill of reservoir • Failure of protective packaging (moisture ingress)	2	3	4	24	

[1] Based on underlying assumption that patients use the device as intended (human factors 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, thus an intermediate value of 3 is assigned

Final Drug Product Risk Assessment - Attachment

	• Particle size distribution of FP • Amorphous content of FP • Device malfunction • Particle size/amorphous content of lactose • Static charge of formulation • Composition of device air flow path components • Device flow resistance variation • Incorrect lactose grade used (b) (4)) for a product strength					(b) (4)
Purity (impurities/degradants)	• Degradation of API as formulated • Input purity of FP • Input purity of lactose • Incompatibility of FP with lactose • Incompatibility of formulation with device components in long-term contact	1	3	2	6	

Craig Bertha, ATL (19-DEC-2016)

Craig Bertha

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Date: 12/19/2016 09:10:17AM
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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)

Date:	September 26, 2016 **(Updated 11/1/2016)**
To:	Art Shaw, CDER, OPQ, ONDP, Arthur.Shaw@fda.hhs.gov
CC:	Office of Combination Product at: combination@fda.gov Regulatory Business Program Manager (RBPM)/Regulatory Program Manager (RPM): Florence Aisida E-Mail: Bamidele.Aisida@fda.hhs.gov CDER/OPQ/OPF: Juandria.Williams@fda.hhs.gov
Through:	Francisco Vicenty, REGO/DMQ/OC, CDRH, WO 66, Rm 3426, E-mail: Francisco.Vicenty@fda.hhs.gov Rakhi Dalal, REGO/DMQ/OC, CDRH, WO 66, Rm 3454, E-mail: Rakhi.Dalal@fda.hhs.gov Rakhi M. Panguluri -S Digitally signed by Rakhi M.Panguluri -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13002002 1, cn=Rakhi M. Panguluri -S Date: 2016.12.01 08:35:30 -05'00'
From:	Crystal Lewis, REGO/DMQ/OC, CDRH, WO 66, Rm 3452, E-mail: Crystal.lewis@fda.hhs.gov
Applicant/Licensure:	Teva Pharmaceutical Industries Ltd. 5 Basel Street Petach Tikva, Israel 4951033 FEI: 3002874027
Submission (Type & Number):	NDA 208798
Combination Product Name:	Fluticasone propionate
Combination Product Intended Use:	Product is intended for the treatment of asthma as a prophylactic therapy.
Device Constituent (Type):	Multidose Dry Powder Inhaler (MDPI)
ICCR Number:	ICC1600240
ICCR Instruction (ICCR Form):	Consultative Review
Pre-Approval Facility Inspection:	No See Inspection Guidance, ICCR Memo date, Page #14
Documentation Review	**Complete**
CDRH/OC Recommendation:	**Approvable**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of Fluticasone propionate, NDA 208798.

PRODUCT DESCRIPTION

Fluticasone propionate is the active pharmaceutical ingredient of the multidose dry powder inhaler (Fp MDPI). The MDPI is the primary container closure system and consists of an inspiratory flow driven device that contains a reservoir. Together, fluticasone proprionate and the MDPI form the combination product (CP). The CP is utilized for the treatment of asthma as prophylactic therapy. The Fp MDPI is provided in three strengths 55mcg, 113mcg, and 232mcg. Each strength of the Fp MDPI delivers 60 actuations and one actuation represents one therapeutic dose of the drug product, see figure 1 below.

The Fp MDPI device consists of (b) (4) (b) (4) (b) (4) (b) (4) These documents are found in section 3.2.P.2.4 Container Closure System. Figure 1 provides an illustration of the Fp MDPI device indicating the location of the sub-assemblies.

Figure 1: Functional Representation of the Fp MDPI Device

(b) (4)

REGULATORY HISTORY

The following facility was identified as being subject to applicable Quality System Requirements under 21 CFR part 820 and 21CFR Part 4.4:

1. Teva Pharmaceutical Industries Ltd.
   5 Basel Street
   Petach Tikva, Israel
   4951033
   FEI: 3002874027

Responsibility – This manufacturer is the NDA 208798 holder and applicant and should conform to 21 CFR Part 4 for the finished combination product. This is also the correspondence address for the firm. No inspectional history is available for the applicant at FEI# 3002874027. CDRH/OC recommends a post-approval inspection of the applicant at FEI 3002874027.

Inspection Recommendation:
An inspection is not required because:

- No manufacturing activity for the combination product occurs at this site.

2. IVAX Pharmaceuticals (aka Teva Pharmaceuticals Ireland)
   Unit 301 Industrial Park, Cork Road
   Waterford, Ireland 999999
   FEI # 3002807777

Responsibility – This manufacturer is responsible for the testing and release of raw materials, device and packaging components. This facility also performs manufacturing, packaging and in-process testing of the finished product. Testing and release of finished product, stability testing of finished product and batch release also occurs at this facility.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed an inspection was performed September 7- September 10, 2015. The inspection covered drugs and was classified NAI.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product. Therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance, p. 12).

Inspection Recommendation:
An inspection is not required because:

- A recent medical device inspection of the firm was acceptable.

DOCUMENTATION REVIEW
The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20
(Updated 11/1/16)
The firm has identified Teva Pharmaceuticals Ireland (TPI) as the site with the ultimate responsibility for the overall combination product. Teva's Quality Policy Document defines the

(b) (4)

[redacted]

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

(b) (4)

Design Control, General, 21 CFR 820.30
(Updated 11/1/16)

The MDPI or primary container closure system's design is formulated on a patented pneumatic system. This pneumatic system is utilized in metering the drug contained in the powder blend from the reservoir. A fixed volume dose cup transfers the metered dose to an inhalation position thereby making it available for inhalation. (b) (4) (b) (4) only the metered dose is made available for inhalation. Once available, the metered dose becomes aerosolized and ready for delivery from the device. The device is also designed to prevent overdosing following multiple actuations before inhalation.

Further, the firm describes the design and development of the device being the responsibility of

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Table 13: Release and Stability Specifications for Fluticasone Propionate Inhalation Powder 55, 113 and 232 mcg, 60 Actuations products (Continued)

Test	Acceptance Criteria		
Aerodynamic Particle Size Distribution (APSD) by (b) (4)			
55 mcg	(b) (4)		
113 mcg			
232 mcg			
Device Flow Resistance			
Foreign Particulate Matter	≥ 2 µm and < 10 µm ≤ (b) (4) ≥ 10 µm and < 25 µm ≤ ≥ 25 µm ≤		
Microbiological Examination of Nonsterile Inhalation Products	Total Aerobic Microbial Count (TAMC):	NMT (b) (4) CFU/g	
	Total Combined Yeasts and Moulds Count (TYMC):	NMT (b) (4) CFU/g	
	Bile-tolerant Gram-negative Bacteria:	Absent/g	
	Pseudomonas aeruginosa:	Absent/g	
	Staphylococcus aureus:	Absent/g	

[4] For release only

Documentation Review Recommendation

The application for Fluticasone propionate, NDA 208798 is approvable from the perspective of the applicable Quality System Requirements.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

CDRH/OC RECOMMENDATION

(1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

(2) There were no facility inspections for compliance with applicable Quality System Requirements needed for approvability determination.

Crystal Lewis -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Crystal Lewis -S, 0.9.2342.19200300.100.1.1=2000430186
Date: 2016.12.01 09:23:13 -05'00'

Crystal Lewis

Prepared: Clewis: 9/26/16, 11/1/16, 11/10/16, 11/16/16
Reviewed: RDalal: 9/27/2016, 10/5/2016, 12/01/2016

CTS No.: ICC1600240
NDA 208798

Review Cycle Meeting Attendance:
None

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 208798	**Submission Type: 505(b)(2)**	**Established/Proper Name: fluticasone propionate (FP)**
Applicant: Teva Pharmaceutical Industries Ltd.	**Letter Date: 28-MAR-2016**	**Dosage Form: inhalation powder**
Chemical Type: non-NME (type 5 NDA)	**Stamp Date: 28-MAR-2016**	**Strength: 55, 113, 232 mcg/actuation**

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?		X	

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]	☐	☒	For patients 12 years of age and older
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 _____	☒	☐	
19.	Other _____	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Regulatory Considerations					
20.	USAN Name Assigned		☒	☐	Fluticasone propionate
21.	Meeting Agreements (under IND 108838)		☒	☐	16-NOV-2015, Pre-NDA Meeting: • Agency agreed with the proposed stability data plan (12 months long term and 6 months accelerated at time of submission) • Estimation of the metered dose was a topic of concern both in terms of the number of significant figures and in terms of dose proportionality • There was discussion of the stability program in relation to the switch from the NB7/3 to NB8 version of the device (see minutes for details and proposed comparability protocol, *vide infra*) • There was discussion of the drug product characterization studies proposed for the trade and sample counts (60 vs 28 actuations; see minutes for details) • There was discussion of the qualification of an alternate drug product manufacturing site (see minutes for details)
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☐	Unknown
24.	Comparability Protocol(s)[2]		☒	☐	The application contains a comparability protocol for the switch from the device used in the registration stability batches (NB7/3) to a new device variant with a modified (b) (4) (see P.2.7.3.2); there are three (3) additional comparability protocols included in the R section
25.	Other _____		☐	☐	
Quality Considerations					
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☒	☐	Applicant refers to a (b) (4) process parameters in the P.2 section.
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☐	N/A
33.	Alternative Microbiological Test Methods		☐	☒	Microbiology team can confirm, but testing and acceptance criteria proposed appear consistent with USP <61>, <62> & <1111>
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐	
36.		Excipients	☒	☐	Lactose specification includes additional testing for PSD, assay, impurities/degradants, endotoxins, particle shape and morphology, protein content and morphic form
37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	Lactose comes from bovine milk, so technically that is of animal origin
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☒	☐	Bulk filled inhalers are packaged in (b) (4) in storage containers at 30°C/65%RH for 6 weeks; (b) (4) units are individually wrapped with protective packaging and desiccant prior to release
43.	Genotoxic Impurities or Structural Alerts		☒	☐	Technically all of the listed impurities of FP have a (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]		☐	☒	
48.	Novel BE study designs		☐	☐	Unknown, refer to clinical pharmacology filing review
49.	New product design[1]		☒	☐	The Respiclick device has not been used with an FP formulation before, although another FP inhalation powder of a different design has been approved
50.	Other_____		☐	☐	N/A

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Will not require consult to EA team for review (estimation of EIC)
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	☐	☒	☐	• For the sections examined for the filing review (not all pages of the application were examined) • QOS is only a summary of

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	❑ 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				module 3, thus a review is not necessary (as module 3 will be reviewed) • There is no specific method validation package included, but since this is not an NME and there are no novel methods, it is unlikely that the team will need to send any of the methods to the laboratory for assessment
	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)	☒	☐	☐	Nine (9) sites are listed on Form 356h; note that two site are manufacturers of device components (b) (4)
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				
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☐	☒	☐	The Letter of Authorization from (b) (4) (DMF (b) (4)) does not include US Agent contact information
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	☐	☒	☐	• Follows CTD formatting (note that not all pages of the application were examined) • Application does *not* include production data on the manufacture of the drug substance (no executed batch

C. FILING CONSIDERATIONS					
	○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability ○ Includes data establishing stability of the drug substance through the proposed retest period and a stability protocol describing the test methods used and time intervals for assessment				records for drug substance are included in the regional information section, however, this is not required by regulation under 21 CFR 314.50) • Application does include batch data for drug substance manufactured for the registration batches of the drug product • There is no indication in the NDA that there have been any changes to the manufacturing process for the drug substance (this possibility will need to be examined with review of the associated DMF from (b) (4)) • The applicant refers to the (b) (4) DMF for process validation and evaluation as well as stability data
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development ❑ Manufacture ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product ○ Includes production data on drug product	☐	☒	☐	• Much of the development changes that have and will take place have to do with the device • Table 1 in P.5.4 provides a summary of the usage of the various batches of drug product of each strength (note that one or two batches per strength were used both for clinical and registration stability studies) • Control of the lactose excipient includes additional testing as per Agency recommendations for inhalation powder drug products • Ivax (Teva) Pharmaceuticals Ireland was the site of manufacture for the registration/clinical batches and is the intended commercial site; Teva states that "the process that

C. FILING CONSIDERATIONS					
	manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System ○ Include data outlined in container closure guidance document ❑ Stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				will be validated will be the same as and use similar equipment to that used for the manufacture of the registration batches;" the scale used for these registration stability/clinical batches was (b)(4)kg (the proposed commercial scale) • No data for process validation lots are provided (and this is not typically required for the NDA); process consistency can be judged based on the data from the clinical and registration stability batches • No analytical validation package is included for release test procedures (*vide supra*)
	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? *(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	☐	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	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?	☐	☒	☐	Not every page of the application was examined
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	No executed batch records for drug substance are provided (but this is N/A)
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 marketed with summaries of test results for those samples	☐	☐	☒	

ONDQA Initial Quality Assessment (IQA) and Filing Review

For Pre-Marking Applications

NDA #: 208798 Received Date: 30-MAR-2016

Drug Product Risk Assessment

DP attribute/ CQA	Factors that can impact the CQA[1]	O[2]	S[4, 3]	D[4]	FMECA RPN #	Comment & considerations
Delivered Dose Uniformity (DDU)	• Inhomogeneity or low formulation assay of FP/lactose blend (e.g., from manufacturing; result of shipping) • Lower than target fill of reservoir • Failure of protective packaging (moisture ingress) • Device malfunction • Amorphous content of FP • Particle size/amorphous content of lactose • Static charge of formulation from manufacturing • Bridging of formulation particles (i.e., crystallization of amorphous material)	2	3	4	24	(b) (4) [redacted]

[1] Based on underlying assumption that patients use the device as intended (human factors 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, thus an intermediate value of 3 is assigned

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Drug Product Risk Assessment

Aerodynamic Particle Size Distribution (APSD)	• Inhomogeneity or low assay of FP/lactose blend • Lower than target fill of reservoir • Failure of protective packaging (moisture ingress) • Particle size distribution of FP • Amorphous content of FP • Device malfunction • Particle size/amorphous content of lactose • Static charge of formulation • Composition of device air flow path components • Device flow resistance variation • Incorrect lactose grade used (2 PSD grades) for a product strength	2	3	4	24	(b) (4)
Purity (impurities/degrad	• Degradation of API as formulated	1	3	2	6	

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NDA #: 208798 Received Date: 30-MAR-2016

Drug Product Risk Assessment

ants)	• Input purity of FP • Input purity of lactose • Incompatibility of FP with lactose • Incompatibility of formulation with device components in long-term contact						(b) (4)

Craig Bertha, ATL (4/15/2016)

Craig M. Bertha -S

Digitally signed by Craig M. Bertha -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300103470, cn=Craig M. Bertha -S
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