

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

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**PHARMACOLOGY REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY CHEMISTRY CONSULTATION FOR  
FLUTICASONE PROPIONATE AND FLUTICASONE PROPIONATE/SALMETEROL  
XINAFOATE MULTI-DOSE DRY POWDER INHALERS**

Application number: NDA 208,798/ 208,799

Supporting document/s: SDN#1  
SDN#22  
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December 1, 2016/ November 17, 2016  
December 9, 2016/ December 1, 2016

Product: Fluticasone propionate inhalation powder  
Fluticasone propionate/salmeterol xinafoate  
inhalation powder

Indication: Treatment of asthma as prophylactic therapy in  
patients 12 years of age or older

Applicant: Teva Pharmaceutical Industries Ltd

Review Division: Division of Pulmonary, Allergy, and  
Rheumatology Products

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# 1 Executive Summary

## 1.1 Introduction

The Sponsor submitted the present 505(b)(2) New Drug Applications (NDAs) 208,798/ 208,799 on March 28, 2016 to support the marketing approval of Fluticasone propionate (Fp) inhalation powder and Fluticasone propionate/Salmeterol xinafoate (FS) inhalation powder using a proprietary multidose dry powder inhaler (MDPI), respectively. The FP TRADENAME drug product is an inhalation driven, reservoir-type, multidose dry powder inhaler that is formulated in three strengths, which meter 55, 113, or 232 µg of fluticasone propionate from the device reservoir and deliver 51, 103, or 210 µg of fluticasone propionate, respectively, from the mouthpiece per actuation. The FS TRADENAME drug product (i.e., FS MDPI) is an inhalation driven, reservoir-type, multidose dry powder inhaler that is formulated in three strengths, which meter 55/14, 113/14, or 232/14 µg of fluticasone propionate/salmeterol xinafoate from the device reservoir and deliver 49/ (b) (4), 100 (b) (4), or 202/ (b) (4) µg fluticasone propionate/salmeterol xinafoate, respectively, from the mouthpiece per actuation. Each inhaler is supplied for 60 actuations. This review is a nonclinical safety evaluation of potential leachables and foreign particulate counts for the FP and FS TRADENAME drug products.

## 1.2 Brief Discussion of Nonclinical Findings

There are no safety concerns based on the results from the leachable studies and foreign particulate counts.

# 2 Drug Information

## 2.1 Drug

### Tradename(s)

FP TRADENAME

FS TRADENAME

### Generic Name

Fluticasone propionate

Fluticasone propionate/Salmeterol xinafoate

### Chemical Name

Fluticasone propionate: S-(fluoromethyl)6(alpha),9-difluoro-11(beta)-17-dihydroxy-16(alpha)-methyl-3-oxoandrosra-1,4-diene-17(beta)-carbothioate, 17-propionate

Salmeterol xinafoate: 4-hydroxy-α'-[[[6-4-phenylbutoxyl)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthelene carboxylate

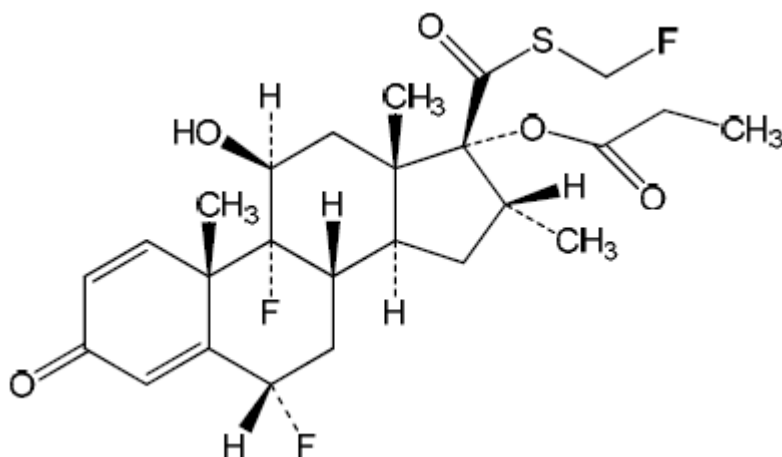
**Molecular Formula/Molecular Weight**

Fluticasone propionate:  $C_{25}H_{31}F_3O_5S$ / 500.6 g/mole

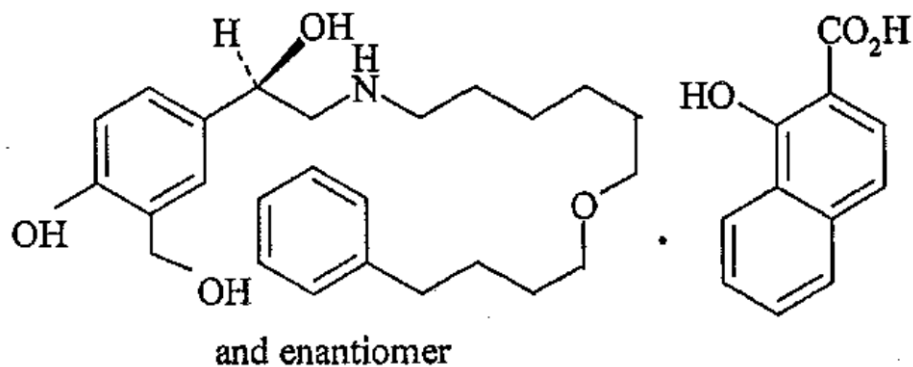
Salmeterol xinafoate:  $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$ / 603.8

**Structure or Biochemical Description**

Fluticasone propionate:



Salmeterol xinafoate:

**Pharmacologic Class**

Fluticasone propionate: Corticosteroid

Salmeterol xinafoate: Long acting  $\beta_2$ -adrenergic agonist

**2.2 Relevant INDs, NDAs, BLAs and DMFs**

IND 108838: Teva, Fluticasone propionate

IND 072240: Teva, Fluticasone propionate/salmeterol

NDA 20833: GSK, Flovent<sup>®</sup> Diskus<sup>®</sup>

NDA 21433: GSK, Flovent<sup>®</sup> HFA

NDA 21077: GSK, ADVAIR DISKUS

## 2.3 Drug Formulation

The Sponsor's proposed drug product (i.e., fluticasone propionate multidose dry powder inhaler [Fp MDPI]), is an inhalation driven, reservoir-type, multidose dry powder inhaler containing a blend of fluticasone propionate as the active pharmaceutical ingredient and alpha lactose monohydrate (which may contain milk proteins) as the excipient (see table 1). The products are formulated in three strengths, which meter 55, 113, or 232 µg of fluticasone propionate from the device reservoir and deliver 51, 103, or 210 µg of fluticasone propionate, respectively, from the mouthpiece per actuation. Each actuation represents one therapeutic dose of the product. Each inhaler is supplied for 60 actuations.

The Sponsor's proposed drug product (i.e., fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler [FS MDPI]), is an inhalation driven, reservoir type, multidose dry powder inhaler containing a blend of fluticasone propionate and salmeterol xinafoate as the active pharmaceutical ingredients, and lactose monohydrate as the excipient (see Table 2). The products are formulated in three strengths, which meter 55/14, 113/14, or 232/14 µg of fluticasone propionate/salmeterol xinafoate from the device reservoir and deliver 49/ (b) (4), 100 (b) (4), or 202/ (b) (4) µg fluticasone propionate/salmeterol xinafoate, respectively, from the mouthpiece per actuation. Each actuation represents one therapeutic dose of the product. Each inhaler is supplied for 60 actuations.

(Excerpt from Sponsor's submission)

**Table 1. Composition of each emitted actuation from Fp MDPI products**

| Ingredient                         | Emitted Quantity <sup>a</sup> |         |         |
|------------------------------------|-------------------------------|---------|---------|
|                                    | 55 mcg                        | 113 mcg | 232 mcg |
| Fluticasone propionate,<br>(b) (4) | 51 mcg                        | 103 mcg | 210 mcg |
| Lactose monohydrate                | (b) (4)                       |         |         |

<sup>a</sup> This is based on a theoretical weight of (b) (4) per actuation.

(Excerpt from Sponsor's submission)

**Table 2. Composition of each emitted actuation from FS MDPI products**

| Ingredient                         | 55/14 mcg <sup>a</sup> | 113/14 mcg <sup>a</sup> | 232/14 mcg <sup>a</sup> |
|------------------------------------|------------------------|-------------------------|-------------------------|
| Fluticasone propionate, micronized | 49 mcg                 | 100 mcg                 | 202 mcg                 |
| Salmeterol xinafoate, micronized   | 18.52 mcg <sup>b</sup> | 18.52 mcg <sup>b</sup>  | 18.52 mcg <sup>b</sup>  |
| Lactose monohydrate                | (b) (4)                |                         |                         |

<sup>a</sup> This is based on a theoretical weight of (b) (4) per actuation<sup>b</sup> 18.52 mcg of salmeterol xinafoate is equivalent to 12.75 mcg of salmeterol base.

## 2.4 Comments on Novel Excipients

There are no novel excipients in the drug formulations.

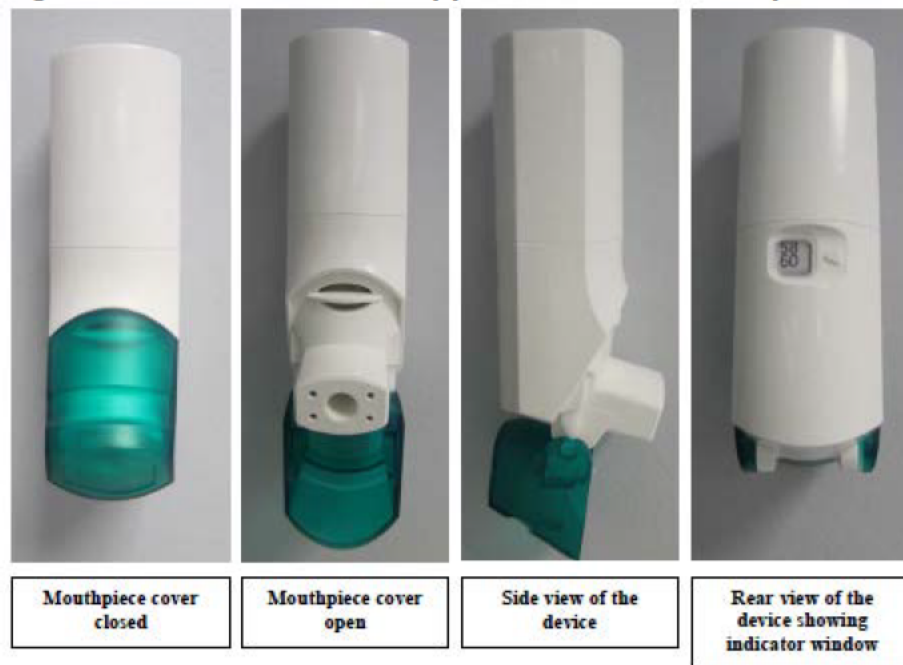
## 2.5 Comments on Extractables and Leachables Studies

This review is a nonclinical safety evaluation of potential leachables and observed foreign particulates for the FP and FS MDPI drug products. Described in this section are the studies and the results; the nonclinical safety evaluation is included in the **Integrated Summary and Safety Evaluation** section.

Fluticasone propionate inhalation powder (also known as fluticasone propionate multidose dry powder inhaler [FP MDPI]) is a reservoir type, inspiratory flow driven, multidose dry powder inhaler containing a drug-lactose blend. The primary container closure system is the MDPI, the design of which is based on a patented pneumatic system to meter the drug-containing powder blend from the powder-containing reservoir to a fixed volume dose cup and then transfer the metered dose to an inhalation position to make it available for inhalation. Fluticasone propionate/salmeterol xinafoate inhalation powder (also known as fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler [FS MDPI]) uses an identical device.

(Excerpt from Sponsor's submission)

**Figure 1. FP MDPI external appearance with mouthpiece cover open and closed**



The Fp MDPI device consists of a

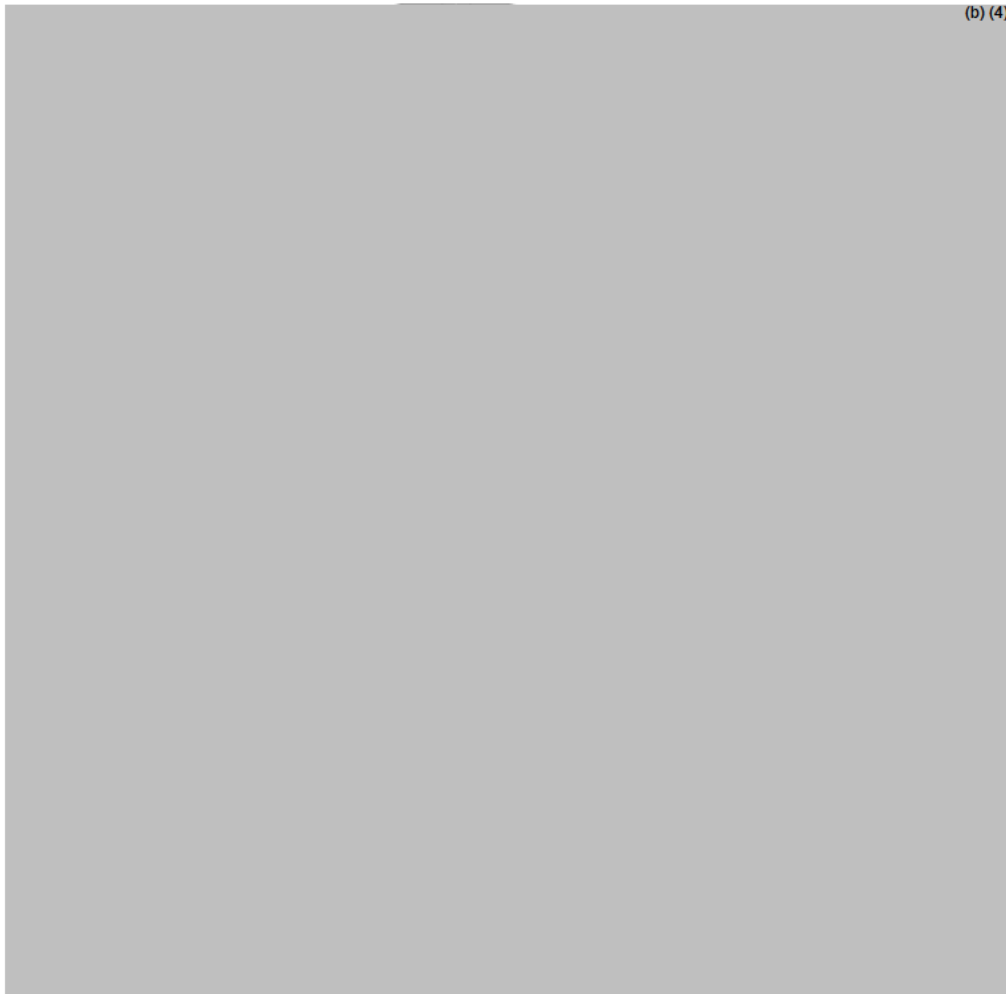
(b) (4)

The primary device components, i.e. those in contact with the formulation, with the exception of the

(b) (4)

(Excerpt from Sponsor's submission)

**Figure 2. Cross-sectional view of key FP MDPI device components**



Extractables Testing Strategy: Component parts were identified as critical if they either have contact with the drug formulation or with patient mucosa. These components were identified as having the highest potential to introduce chemical species to the patient. Component parts were subjected to extreme/aggressive extraction conditions with and without solvent contact. The chemicals evolved or extracted were analyzed and identified.

(Excerpt from Sponsor's submission)

**Table 3. Critical inhaler components****Table 2: Critical Inhaler Components**

| Class (Contact)                                                      | Component name | Material | Function                           |
|----------------------------------------------------------------------|----------------|----------|------------------------------------|
| Class 1<br>(Continuous contact with drug formulation)                | (b) (4)        | (b) (4)  | Reservoir to store powder          |
|                                                                      |                |          | Lid to contain powder in reservoir |
|                                                                      |                |          | Receives metered dose              |
| Class 2 (Transient contact with drug formulation)                    | (b) (4)        | (b) (4)  | (b) (4)                            |
|                                                                      |                |          | (b) (4)                            |
| Class 3 (Transient contact with drug formulation and patient mucosa) |                |          | (b) (4)                            |
| Class 4 (Contact with patient mucosa)                                | (b) (4)        | (b) (4)  | Outer packaging assembly           |

The design of the extractables assessment was based on the PQRI concept of the Safety Concern Threshold (SCT), which indicates that any compound below the level of 0.15 mcg per day by inhalation would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects.

For Fluticasone propionate inhalation powder product, this threshold was applied to components in continuous contact with the drug product, specifically, (b) (4)

A second threshold was applied to components in transient contact with the drug formulation, with or without contact to the patient. This threshold is 20 mcg per gram of component (PQRI Best Practices document, line 4228). This higher threshold level is due to the reduced likelihood for leaching.

For Fluticasone propionate inhalation powder product, this threshold was applied to extractables from the (b) (4) and for secondary packaging components, foil pouch and desiccant.

Each of these thresholds was converted into an Analytical Evaluation Threshold (AET) calculated for each component of an orally inhaled drug product, based on component weight, number of doses of drug formulation per day per user and total number of doses per device.

The extractables assessment includes a number of methodologies that determine the volatiles, semi-volatiles, and non-volatile organic compounds and elemental species that are extracted from each component. Components were subjected to extreme temperatures, both with and without solvent, to extract chemical species that could potentially migrate into the patient by the drug formulation, or from the device materials themselves.

(Excerpt from Sponsor's submission)

**Table 4. Analytical techniques and sample preparation for extractables assessment**

**Table 5: Analytical Techniques and Sample Preparation for Extractables Assessment**

| Reference Section | Chemicals Detected                                                                                     | Analytical Technique                                                                    | Sample Preparation                                                                                                                                                                           |
|-------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Section 4.3.1     | Volatile organic compounds (molecular weight range of approximately 30 to 250 atomic mass units)       | Static headspace gas chromatography mass spectrometry detector                          | Device components are heated within a sealed vial to release volatiles chemicals                                                                                                             |
| Section 4.3.2     | Semi-volatile organic compounds (molecular weight range of approximately 30 to 600 atomic mass units)  | Solvent injection gas chromatography mass spectrometry detector                         | Device components are heated in the presence of polar, mid-polar and non-polar solvent (water, isopropyl alcohol and hexane) for the extraction of semi-volatiles and non-volatile chemicals |
|                   | Non-volatile organic compounds (molecular weight range of approximately 200 to 1400 atomic mass units) | Solvent injection liquid chromatography with ultraviolet and mass spectrometry detector |                                                                                                                                                                                              |
| Section 4.3.3     | Methodology for screening of elements                                                                  | Inductively coupled plasma with mass spectrometry detector                              | Device components are heated in the presence of water and nitric acid for the extraction of elemental species                                                                                |

### Volatiles Extractables Assessment

For Fluticasone propionate inhalation powder product, volatile compounds were of the highest risk for introduction to the patient. Volatile compounds have a low molecular weight and therefore, were most likely to migrate as they require lower energy to pass directly from the component into the patient, or indirectly from the component into the drug formulation and then into the patient.

For this assessment, each component was placed into individual sealed headspace vials stored at 90°C for 24 hours prior to analysis; any volatiles produced were then injected into a gas chromatograph and detected using a mass spectrometer.

**Semi-Volatiles and Non-Volatile Extractables Assessment**

Analysis of semi-volatile and non-volatile organic extractable compounds was performed using a variety of solvents, with different polarity, in order to assess a broad range of extractables species. Each sample component was individually reflux extracted for 24 hours using water, isopropanol and hexane. Each extract was analyzed using gas and liquid chromatographic techniques combined with mass spectrometry detection.

**Elemental Extractables Assessment**

To assess elemental extractables, each critical component part was extracted in 2% nitric acid aqueous solution and separately in water at 90°C for 24 hours.

**LEACHABLES ASSESSMENT**

A leachables assessment was conducted to determine the risk of exposure to the patient. The leachables assessment will also identify if any other species have migrated into the drug formulation from non-contact components under stability. Five target leachables were selected based on abundance in the component extractables evaluation and in an aged sample analyzed during development (b) (4)

The SCT was converted into an AET based on the number of doses per day and number of doses per device. All compounds detected over the Safety Concern Threshold were toxicologically evaluated. Very few extractables compounds were detected as leachables.

**Leachable Studies**

A leachables assessment was conducted on three low strength batches of fluticasone propionate (55 mcg, 60 actuations) and fluticasone propionate/salmeterol xinafoate (55/14 mcg, 60 actuations) inhalation powder. The drug product was wrapped and stored in both upright and inverted orientations under ICH stability conditions. A summary of the FP and FS leachables stability programs are shown in the tables below.

A leachable study also evaluated compounds that had leached in aged Fluticasone propionate (FP) and Fluticasone propionate/salmeterol xinafoate (FS) MDPI 60 Dose drug products stored for 6 months in two orientations (upright and inverted)/wrapped and under accelerated stability conditions.

(Excerpt from Sponsor's submission)

**Table 5. Summary of FP MDPI leachables stability program**

| Product / Strength                                               | Batch number           | Storage orientation  | Conditions                                               | Leachables Testing Schedule      |
|------------------------------------------------------------------|------------------------|----------------------|----------------------------------------------------------|----------------------------------|
| Fluticasone propionate inhalation powder / 55 mcg, 60 actuations | RD1404, RD1407, RD1412 | Upright and Inverted | 25°C/60% RH (Controlled Room Temperature (CRT)), wrapped | 0, 3, 6, 9, 12, 18 and 36 months |
|                                                                  |                        |                      | 40°C/75% RH (Accelerated (ACC)), wrapped                 | 0, 3 and 6 months                |

(Excerpt from Sponsor's submission)

**Table 6. Summary of FS MDPI leachables stability program**

| Product / Strength                                                             | Batch number           | Storage orientation  | Conditions                                               | Leachables Testing Schedule          |
|--------------------------------------------------------------------------------|------------------------|----------------------|----------------------------------------------------------|--------------------------------------|
| Fluticasone propionate/salmeterol inhalation powder / 55/14 mcg, 60 actuations | FS2004, FS2005, FS2006 | Upright and Inverted | 25°C/60% RH (Controlled Room Temperature (CRT)), wrapped | 0, 3, 6, 9, 12, 18, 24 and 36 months |
|                                                                                |                        |                      | 40°C/75% RH (Accelerated (ACC)), wrapped                 | 0, 3 and 6 months                    |

**1. Stability Assessment** (b) (4) Project No. 059669-01-03; Study no. QDP0094645)

The leachable studies evaluated compounds that had leached from the MDPI device into the Fluticasone propionate drug product. The FP MDPI leachables assessment evaluated multiple lots of drug product for up to 6 months under accelerated (40°C/75% relative humidity [RH]) and controlled room temperature (25°C/60% relative humidity) conditions. The lots were evaluated by High Performance Liquid Chromatography (HPLC) and Gas Chromatography/Flame Ionization Detector (GC/FID).

**HPLC**

HPLC identified the presence of (b) (4) in the initial testing sample (0 months) of (b) (4) µg/g (Lot RD1412). The Sponsor's report stated that unexpected findings were observed for (b) (4) at the 3-month time point compared to the initial results from FP MDPI. Additional testing for (b) (4) was performed from three inhalers obtained from reserve samples. At the 6-month time point, (b) (4) (inverted) and (b) (4) (upright) µg/g was detected.

GC/FID

GC/FID analysis revealed the presence of (b) (4) in the initial testing sample (b) (4) µg/g) and 3- and 6-month samples under both temperature conditions (Lot no. RD1404).

2. Aged Product Assessment (b) (4) Project No. 060491-01-01;  
Study No. QDP0094633)

A leachable study evaluated compounds that had leached in aged Fluticasone propionate (FP) and Fluticasone propionate/salmeterol xinafoate (FS) MDPI 60 Dose drug products stored for 6 months in two orientations (upright and inverted)/wrapped and under accelerated stability conditions 40°C/75% RH. The lots were evaluated by HPLC and GC/FID.

HPLC

HPLC identified the presence of (b) (4) as a leachable in the FS sample at a maximum concentration of (b) (4) µg/g.

GC/FID

GC/FID analysis revealed the presence of (b) (4) in the FP and FS samples at maximum concentrations of (b) (4) µg/g, respectively.

3. Aged Fluticasone propionate in MDPI Assessment (b) (4) Project No. 057172-01-01;  
Study no. QDP0099165)

Aged Fluticasone propionate in MDPI stored at 25°C/60% RH, inverted and 40°C/75% RH, inverted (for approximately 12 months) were analyzed for the screening of leachables. Headspace gas chromatography-mass spectrometry (HS/GC/MS), direct injection gas chromatography-mass spectrometry (GC/MS), ultra-high performance liquid chromatography with both mass spectrometer and ultraviolet detectors (UHPLC/UV/MS) and inductively couple plasma mass spectrometry (ICP/MS) methods were utilized for the qualitative and semi-quantitative determination of the leachables.

The Sponsor, using a PQRI safety concern threshold (SCT) of (b) (4) µg/day, calculated an Analytical Evaluation Threshold (AET) of (b) (4) µg/device. Briefly, the formulation for the product contains FP at 50 µg per actuation, with 2 actuations per day per user. The product contains 60 doses per device. The Sponsor's calculated AET is a very conservative level.

HS/GC/MS

HS/GC/MS did not identify any compounds above the AET.

GC/MS

GC/MS determined the presence of (b) (4) as a leachable at an estimated maximum concentration of (b) (4) µg/device.

UHPLC/UV/MS

UHPLC/UV/MS analysis determined non-volatile compounds as leachables.

UHPLC/UV/MS identified (b) (4) µg/device) and (b) (4) (b) (4) µg/device) as leachables above the calculated AET.

ICP/MS

ICP/MS did not identify any leachable elements.

Summary of Leachable Studies:

At total of five compounds were tracked as leachables for nine months during the stability study. Only compounds (b) (4) were reported throughout the study. Compounds (b) (4) were targeted as leachables but were not detected above the limit of quantitation for the method. A summary of quantifiable leachable compounds detected in the FP and FS MDPI drug product is shown in the table below.

**Table 7. Quantifiable leachable results for FP and FS drug products**

| Compound | Maximum Leachable Concentration (mcg/g) | Maximum Human Exposure <sup>A</sup> (mcg/day) |
|----------|-----------------------------------------|-----------------------------------------------|
| (b) (4)  | (b) (4)                                 | (b) (4)                                       |
| (b) (4)  | (b) (4) mcg/g                           | (b) (4)                                       |
| (b) (4)  | (b) (4) µg/device                       | (b) (4)                                       |
| (b) (4)  | (b) (4)                                 | (b) (4)                                       |
| (b) (4)  | (b) (4) µg/device                       | (b) (4)                                       |

Exposures (mcg/day) were calculated from the leachables data by multiplying the leachable amount (mcg/g) by the approximate weight of the formulation per inhaler (b) (4) g) and the maximum number of actuations per day (2/day), then dividing by the total number of actuations per inhaler (60/inhaler).

**Foreign Particulates**

Stability studies were conducted on 3 registration batches of each dose strength of FP and FS MDPI to evaluate and confirm the long-term stability of the drug product. The nine registration batches were stored at 40°C/75%RH (ACC) for up to 6 months, at 30°C/65%RH (INT) up to 12 months, and will continue to be stored at 25°C/60%RH (CRT) for up to 36 months. The inhalers are stored in the upright and inverted orientations at each storage condition.

Stability studies were also conducted on 1 clinical batch of each dose strength of FP and FS inhalation powder. The three phase 3 clinical batches RD1318, RD1315, and RD1316 were stored at 40°C/75%RH (ACC) for up to 6 months and will continue to be stored at 25°C/60%RH (CRT) for up to 18 months.

The particulate matter was quantified and characterized using Raman microscopy and SEM/EDX techniques. Up to 10 actuations were collected from the inhalers, dissolved in a mixture of methanol, acetonitrile, and water, and filtered to collect the foreign particulate matter for identification. The Sponsor's report stated that the majority of particles analyzed were identified as (b) (4)

The FS and FP MDPI drug product release and stability acceptance criteria for foreign particulates with a (b) (4) diameter between 2 and 10 microns have been proposed to be < (b) (4) counts per actuation. The acceptance criteria for foreign particulates in stability assessments are provided in the table below.

(Excerpt from Sponsor's submission)

**Table 8. Foreign particulates acceptance criteria for FS and FP drug products**

| Particle Size Range    | Counts per Actuation |
|------------------------|----------------------|
| $\geq 2 < 10$ microns  | (b) (4) counts       |
| $\geq 10 < 25$ microns | (b) (4) counts       |
| $\geq 25$ microns      | (b) (4) counts       |

#### 1. FP MDPI

All foreign particulate counts were within the specification limits. Counts of foreign particulates were recorded for particulates measuring between 2 and less than 10 microns, between 10 and less than 25 microns and 25 microns and larger.

For this safety assessment, only particles in the size range up to 10 microns are considered as these particles are most likely to be inhaled and deposited in the lower respiratory tract. The majority of the foreign particulates observed in the stability assessments had geometric size  $\leq 10$  microns.

#### 55 mcg FP MDPI Batches

A total of (b) (4) determinations of foreign particulates counts were obtained from three registration batches. For both ICH and in-use stability, all foreign particulates counts for inhalers stored from 0-12 months were below specification limits. For foreign particulates between 2 and less than 10 microns at each time point and orientation from wrapped inhalers stored up to 6 months at 40°C/75% RH, the counts from individual inhalers ranged from (b) (4) counts, with means ranging from (b) (4) counts. At 25°C/60%RH, the counts of foreign particulates of individual inhalers stored up to 15 or 18 months at CRT ranged from (b) (4) counts, with means ranging from (b) (4) counts.

#### 113 mcg FP MDPI Batches

A total of (b) (4) determinations of foreign particulates counts were obtained from three registration batches. For ICH stability in both orientations (i.e., up and inverted), all foreign particulates counts for inhalers stored from 0-18 months were below

specification limits. For foreign particulates between 2 and less than 10 microns at each time point and orientation from wrapped inhalers stored up to 6 months at 40°C/75% RH, the counts from individual inhalers ranged from (b) (4) counts, with means ranging from (b) (4) counts. At 25°C/60%RH, the counts of foreign particulates of individual inhalers stored 0 to 18 months at CRT ranged from (b) (4) counts, with means ranging from (b) (4) counts.

### 232 mcg FP MDPI Batches

A total of (b) (4) determinations of foreign particulates counts were obtained from three registration batches. For both ICH and in-use stability, all foreign particulates counts for inhalers stored from 0-18 months were below specification limits. For foreign particulates between 2 and less than 10 microns at each time point and orientation from wrapped inhalers stored up to 6 months at 40°C/75% RH, the counts from individual inhalers ranged from (b) (4) counts, with means ranging from (b) (4) counts. At 25°C/60%RH, the counts of foreign particulates of individual inhalers stored up to (b) (4) months at CRT ranged from (b) (4) counts, with means ranging from (b) (4) counts.

## 2. FS MDPI

Counts of foreign particulates were recorded for particulates measuring between 2 and less than 10 microns, between 10 and less than 25 microns and 25 microns and larger. All foreign particulate counts for all three registration batches were below the specification limit for each orientation.

An assessment of the stability trends of foreign particulate matter was conducted for the FP and FS MDPI products. These products use the same device and excipient, but differ in the weight of the formulation delivered per actuation. The Sponsor's report stated that each actuation from the FP product has a mass of (b) (4) mg while each actuation from the FS product has a mass of (b) (4) mg. No difference in the stability trends for foreign particulates was observed between the FP and FS products when the foreign particulate matter was evaluated on a per unit weight per actuation basis.

## **3 Studies Submitted**

### **3.1 Studies Reviewed**

| <b>Title</b>                                                                                                                                                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Toxicology Review and Risk Assessment of the Leachables Profile from the Fluticasone Propionate Multi-Dose Dry Powder Inhaler Drug Product (Document No. NCL0005303)                                            |
| Six Month Cumulative Stability Test Results for Analysis of Leachables in Fluticasone Propionate Drug Product from the MDPI Device (b) (4) Project No. 059669-01-03; Study no. QDP0094645)                      |
| Six Month Cumulative Stability Test Results for Analysis of Leachables in Fluticasone Propionate/Salmeterol Xinafoate Drug Product from the MDPI Device (b) (4) Project No. 059669-01-03; Study no. QDP0094644) |
| Test Results for the Analysis of Leachables in Aged Fluticasone Propionate and Fluticasone                                                                                                                      |

|                                                                                                                |                                                 |
|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| Propionate/Salmeterol Xinafoate MDPI Drug Products (b) (4)                                                     | Project No. 060491-01-01; Study no. QDP0094633) |
| Report for the Leachable Screening of the Aged Fluticasone Propionate in Multi-dose Dry Powder Inhaler (b) (4) | Project No. 057172-01-01; Study no. QDP0099165) |

## 11 Integrated Summary and Safety Evaluation

This review provides a safety assessment of potential leachables and foreign particulate counts from the primary closed container system for the Fp and FS MDPI drug products, based on data submitted by the Sponsor.

In general, for leachable evaluations, compounds with expected patient exposure below the PQRI Thresholds of (b) (4) mcg/day (for sensitizer and irritants, non-genotoxic/non-carcinogen) and (b) (4) mcg/day (for compounds with genotoxic/carcinogenic potential) were considered qualified for safety.<sup>1</sup>

### Leachables Assessment

A leachables assessment was conducted on three low strength batches of fluticasone propionate (55 mcg, 60 actuations) and fluticasone propionate/salmeterol xinafoate (55/14 mcg, 60 actuations) inhalation powder. The drug product was wrapped and stored in both upright and inverted orientations under ICH stability conditions.

Five compounds were tracked as leachables for nine months during the stability study. The compounds (b) (4) were reported throughout the study. The Sponsor stated that (b) (4) were targeted as leachables but were not detected above the limit of quantitation for the method. However, HPLC analysis identified the presence of (b) (4) as a leachable in an FS sample at a maximum concentration of (b) (4) µg/g in an aged product assessment of FS MDPI 60 Dose drug products stored for 6 months in two orientations (upright and inverted)/wrapped and under accelerated stability conditions 40°C/75% RH (Study no. QDP0094633).

No leachable compound was identified at a level that exceeded the PQRI threshold of (b) (4) mcg/day. Overall, there appear to be no safety concerns for the FP and FS MDPI drug products as described in the leachable studies for the container closure system. It should be noted that the expectation for leachables with a dry powder inhaler is very low, which was verified by the Sponsor's results.

Routine extractables testing will be used to control incoming components and component manufacturing processes, to ensure the continued quality of the component parts and monitor any batch-to-batch variability. In addition to the known leachables,

<sup>1</sup> Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products. Product Quality Research Institute. August 2006.

extractables which were abundant in the extractables profile will also be monitored to ensure consistency of the components. Compounds for routine control were selected based on toxicological safety, whether the compounds leached into the formulation or abundance during extractables studies.

Compounds included for routine monitoring are listed below. All leachables will be monitored by routine extractables testing of inhaler components.

(Excerpt from Sponsor's submission)

**Table 9. Compounds selected for routine extractables controls**

**Table 18: Compounds Selected for Routine Extractables Controls**

| Component | Target compounds | Reason for selection                                                               |
|-----------|------------------|------------------------------------------------------------------------------------|
|           | (b) (4)          | Potential source of additional chemical identified in the leachables study (b) (4) |
|           |                  | Ensure consistency of the component material                                       |
|           |                  | Potential leachable                                                                |
|           |                  | Potential source of additional chemical identified in the leachables study (b) (4) |
|           |                  | Ensure consistency of the component material                                       |
|           |                  | Leachable                                                                          |
|           |                  | Ensure consistency of the component material                                       |
|           |                  | Ensure consistency of the component material                                       |
|           |                  | Ensure consistency of the component material                                       |
|           |                  | Ensure consistency of the component material                                       |

**Table 18: Compounds Selected for Routine Extractables Controls (Continued)**

| Component | Target compounds | Reason for selection                         |
|-----------|------------------|----------------------------------------------|
|           | (b) (4)          | Safety of the material                       |
|           |                  | Ensure consistency of the component material |
|           |                  | Ensure consistency of the component material |
|           |                  |                                              |
|           |                  | Ensure consistency of the component material |
|           |                  | Ensure consistency of the component material |
|           |                  | Ensure consistency of the component material |
|           |                  | Ensure consistency of the component material |
|           |                  | Ensure consistency of the component material |
|           |                  | Ensure consistency of the component material |
|           |                  | Leachable                                    |
|           |                  | Ensure consistency of the component material |

**Foreign Particulates Assessment**

For this safety assessment, only particles in the size range up to 10 microns are considered as these particles are most likely to be inhaled and deposited in the lower respiratory tract.

A Chemistry, Manufacturing, and Control Information Request forwarded to the Sponsor on November 8, 2016 requested an analysis of the proposed specifications for foreign particulate matter from a safety point of view. It was noted that the acceptance criteria were significantly greater than the observed data, as well as above the acceptance criteria in the USP monographs for Fluticasone propionate inhalation powder and fluticasone propionate and salmeterol xinafoate inhalation powder. The Sponsor provided an analysis of the proposed specifications for foreign particulate matter from a safety perspective. The Sponsor stated that the current proposed specifications do not appear to pose a significant risk to patient safety; however, a limited number of batches have been manufactured with the commercial process. The Sponsor has committed to re-assess the acceptance criteria of the foreign particulate matter after testing ten commercial batches of each strength.

The FS and FP MDPI drug product release and stability acceptance criteria for foreign particulates with a (b) (4) diameter between 2 and 10 microns have been proposed to be < (b) (4) counts per actuation. In stability assessments, all foreign particulates counts for all three sizes for inhalers stored from 0-12 months were below

specification limits. The majority of the foreign particulates observed in the stability assessments had geometric size  $\leq 10$  microns.

To determine the weight of the daily exposure to foreign particulates, it was assumed that the respirable particle size was  $< 10$  mcm and particles were spherical. Mass (M) was calculated assuming a 9 mcm diameter particle using the following equation:

$$M = pV; \text{ where } p = 1 \text{ g/mL and } V = \frac{4}{3}\pi r^3, \text{ where } r = \frac{9}{2} \text{ mcm}$$

$$M = pV = \frac{4}{3}\pi r^3 \text{ g/mL} = \frac{4}{3}\pi \left(\frac{9}{2}\right)^3 \text{ mg}$$

Daily exposure was calculated assuming a maximum of 2 actuations/day using the following calculation:

$$M = \frac{4}{3}\pi r^3 \text{ mg} \times \text{particles/actuation} \times 2 \text{ actuations/day} = \frac{4}{3}\pi \left(\frac{9}{2}\right)^3 \text{ mg/day} = \frac{4}{3}\pi \left(\frac{9}{2}\right)^3 \text{ mcg/day}$$

The current Environment Protection Agency (EPA) standards (24 hr averaging time) for PM-2.5 (particulate matter  $\leq 2.5$  mcm) and PM-10 (particulate matter  $\leq 10$  mcm) are 25 mcg/m<sup>3</sup> and 50 mcg/m<sup>3</sup>, respectively. Therefore, an EPA acceptable daily mass (mcg) of particulate matter for a human respiratory volume of  $\frac{4}{3}\pi r^3$  m<sup>3</sup> (i.e., 2 actuations/day) would be approximately  $\frac{4}{3}\pi r^3$  mcg/day and  $\frac{4}{3}\pi r^3$  mcg/day based on PM-2.5 and PM-10 standards, respectively.

The maximum proposed daily mass of foreign particulates ( $\leq 10$  mcm) from the FS and FP MDPI products at  $\frac{4}{3}\pi r^3$  mcg/day are considered safe relative to the 24-hr particulate concentrations set by the EPA PM-2.5 and PM-10 standards.

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/s/  
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BRETT R JONES  
12/27/2016

TIMOTHY W ROBISON  
12/27/2016  
I concur

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: NDA 208,798  
Supporting document/s: SDN #1  
Applicant's letter date: March 28, 2016  
CDER stamp date: March 28, 2016  
Product: Fluticasone propionate inhalation powder  
Indication: Asthma  
Applicant: Teva Pharmaceutical Industries Ltd  
Review Division: Division of Pulmonary, Allergy, and  
Rheumatology Products  
Reviewer: Brett Jones, PhD  
Supervisor/Team Leader: Timothy Robison, PhD, DABT  
Division Director: Badrul Chowdhury, MD, PhD  
Project Manager: Laura Musse

*Template Version: September 1, 2010*

**Disclaimer**

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# 1 Executive Summary

## 1.1 Introduction

Fluticasone propionate (Fp) oral inhalation powder is an approved drug product indicated for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. It is currently marketed in the U.S. as FLOVENT DISKUS (DPARP; Approval Action on September 29, 2000). The Sponsor submitted the present 505(b)(2) application to support the development of Fluticasone propionate inhalation powder using a proprietary multidose dry powder inhaler (MDPI). The Fp MDPI contains the same active ingredient as FLOVENT DISKUS, which is marketed at strengths of 50, 100, and 250 mcg BID, and is the reference drug.

## 1.2 Brief Discussion of Nonclinical Findings

The Sponsor refers to the Reference Listed Drug, FLOVENT DISKUS, marketed under NDA 20,833, which utilizes the same API and is approved for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older via the oral inhalation route. For this submission, the Sponsor is proposing the Fp MDPI as an inhaled corticosteroid for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age or older. (b) (4)

; however, it is not indicated for the relief of acute bronchospasm.

There is a complete nonclinical program for Fluticasone propionate. No new nonclinical pharmacology or toxicology studies were conducted or required to directly support the safety of Fluticasone propionate. Based upon the Agency's previous findings of safety and efficacy for the reference listed drug, FLOVENT DISKUS, and the public literature, there is sufficient information from the nonclinical perspective to recommend the approval of NDA 208,798.

## 1.3 Recommendations

### 1.3.1 Approvability

NDA 208,798 is recommended for approval from the nonclinical perspective. The label should be modified as shown below.

### 1.3.2 Additional Non Clinical Recommendations

None.

### 1.3.3 Labeling

For this 505(b)(2) submission, the Sponsor provided a label for Fluticasone propionate MDPI (b) (4)

(b) (4)

The Established Pharmacologic Class (under Indications and Usage in the Highlights of Prescribing Information), Section 8.1, Section 8.2, Section 8.3, Section 12.1, and Section 13 were reviewed. See the recommended labeling for the nonclinical section of the product label below.

The Reviewer's recommended labeling is shown below. Additions are shown as underlined text and deletions are shown as strikethrough ~~text~~ with respect to the Sponsor's proposed Fluticasone propionate MDPI label.

## Fluticasone propionate MDPI

### Indications and Usage in the Highlights of Prescribing Information

Fp MDPI is a (b) (4) corticosteroid indicated:

## 8. USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

(b) (4)

There are no randomized clinical (b) (4) studies (b) (4) of FP TRADENAME in pregnant women. There are clinical considerations with the use of FP TRADENAME in pregnant women [see Clinical Considerations]. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight, and/or skeletal variations in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mcg/m<sup>2</sup> basis [see Data]. However, fluticasone propionate administered via inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose approximately 2 times the MRHDID on a mcg/m<sup>2</sup> basis [see Data]. (b) (4)

#### Experience with oral corticosteroids (b) (4)

-suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. The estimated risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. (b) (4)

(b) (4)

Clinical Considerations*Disease-Associated Maternal and/or Embryo/Fetal Risk*

(b) (4)

(b) (4) In women with poorly or moderately controlled asthma, (b) (4) there is an increased risk of several perinatal adverse outcomes such as preeclampsia in the mother and prematurity, low birth weight, and small for gestational age for the neonate. Pregnant women with asthma should be closely monitored (b) (4) and (b) (4) medication adjusted as necessary to maintain optimal asthma control.

(b) (4)

Data

(b) (4)

(b) (4)

### *Animal Data*

In embryofetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate was teratogenic in both species. Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, at a dose approximately 2 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat no observed adverse effect level (NOAEL) was observed at approximately 0.6 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 30 mcg/kg/day).

(b) (4)

Cleft palate and fetal skeletal variations were observed in mouse fetuses at a dose approximately 0.5 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.16 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryofetal development study with pregnant rats dosed by the inhalation route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.5 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0.1 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal inhalation dose of 5.5 mcg/kg/day).

In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reductions of fetal body weights, in the presence of maternal toxicity at doses approximately 0.02 times the MRHDID and higher (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate for 1 fetus at a dose approximately 0.2 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.004 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

(b) (4)

(b) (4)

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

In a pre- and post-natal development study in pregnant rats dosed from late gestation through delivery and lactation (Gestation Day 17 to Postpartum Day 22), fluticasone propionate was not associated with decreases in pup body weight, and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to approximate equivalence to the MRHDID (on a mcg/m<sup>2</sup> basis with maternal subcutaneous doses up to 50 mcg/kg/day).

## 8.2 Lactation

### Risk Summary

There are no available data (b) (4) on the presence of (b) (4) fluticasone propionate in human milk, the effects on the breastfed child, or the effects on milk production, (b) (4)

Other corticosteroids have been detected in human milk. However, fluticasone propionate concentrations in plasma after inhaled therapeutic doses are low and therefore concentrations in human breast milk are likely to be correspondingly low [see Clinical Pharmacology (12.3)]. (b) (4)

he developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FP TRADENAME and any potential adverse effects on the breastfed child from (b) (4) FS TRADENAME or from the underlying maternal condition.

(b) (4)

(b) (4)

(b) (4)

*Animal Data*

Subcutaneous administration (b) (4) of tritiated fluticasone propionate at a dose in lactating rats approximately 0.2 times the MRHDID for adults (on a mcg/m<sup>2</sup> basis) resulted in measurable (b) (4) levels in milk.

(b) (4)

**12. CLINICAL PHARMACOLOGY****12.1 Mechanism of Action**

Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is 18 times that of dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results. The clinical significance of these findings is unknown.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Though effective for the treatment of asthma, corticosteroids do not affect asthma symptoms immediately. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer.

Trials in subjects with asthma have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects with recommended doses of orally inhaled fluticasone propionate. This is explained by a combination of a relatively

high local anti-inflammatory effect, negligible oral systemic bioavailability (less than 1%), and the minimal pharmacological activity of the only metabolite detected in man.

### 13. NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4) -Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 10 times the MRHDID for adults on a mcg/m<sup>2</sup> basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately equivalent to the MRHDID for adults on a mcg/m<sup>2</sup> basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the in vivo mouse micronucleus test.

(b) (4) Fertility and reproductive performance were unaffected in male and female (b) (4) rats at subcutaneous doses up to 50 mcg/kg (approximately equivalent to the MRHDID for adults on a mcg/m<sup>2</sup> basis).  
(b) (4)

## 2 Drug Information

### 2.1 Drug

#### Tradename

FP TRADENAME

#### Generic Name

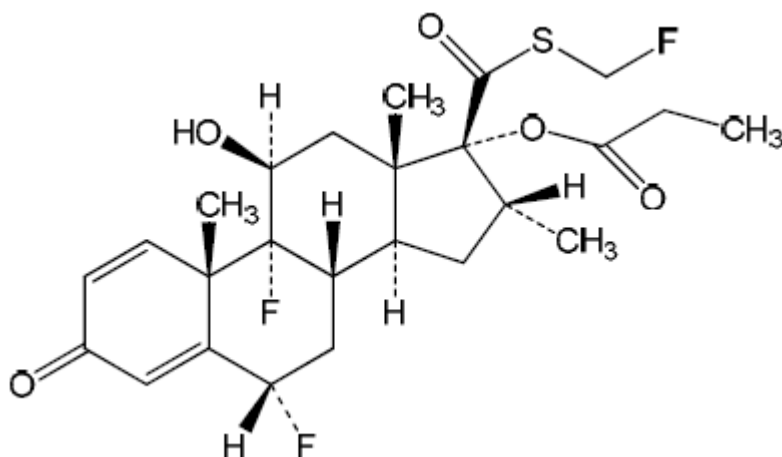
Fluticasone propionate

#### Chemical Name

S-(fluoromethyl)6(alpha),9-difluoro-11(beta)-17-dihydroxy-16(alpha)-methyl-3-oxoandrosra-1,4-diene-17(beta)-carbothioate, 17-propionate

#### Molecular Formula/Molecular Weight

C<sub>25</sub>H<sub>31</sub>F<sub>3</sub>O<sub>5</sub>S/ 500.6 g/mole

**Structure or Biochemical Description****Pharmacologic Class**

Corticosteroid

**2.2 Relevant INDs, NDAs, BLAs and DMFs**

NDA 208799

IND 108838: Teva, Fluticasone propionate

IND 072240: Teva, Fluticasone propionate/salmeterol

NDA 20833: GSK, Flovent<sup>®</sup> Diskus<sup>®</sup>NDA 21433: GSK, Flovent<sup>®</sup> HFA**2.3 Drug Formulation**

The Sponsor's proposed drug product (i.e., fluticasone propionate multidose dry powder inhaler [Fp MDPI]), is an inhalation driven, reservoir-type, multidose dry powder inhaler containing a blend of fluticasone propionate as the active pharmaceutical ingredient and alpha lactose monohydrate (which may contain milk proteins) as the excipient. The products are formulated in three strengths, which meter 55, 113, or 232 µg of fluticasone propionate from the device reservoir and deliver 51, 103, or 210 µg of fluticasone propionate, respectively, from the mouthpiece per actuation. Each actuation represents one therapeutic dose of the product. Each inhaler is supplied for 60 actuations.

(Excerpt from Sponsor's submission)

**Table 1. Composition of each emitted actuation from Fp MDPI products**

| Ingredient                         | Emitted Quantity <sup>a</sup> |         |         |
|------------------------------------|-------------------------------|---------|---------|
|                                    | 55 mcg                        | 113 mcg | 232 mcg |
| Fluticasone propionate,<br>(b) (4) | 51 mcg                        | 103 mcg | 210 mcg |
| Lactose monohydrate                | (b) (4)                       | (b) (4) | (b) (4) |

<sup>a</sup> This is based on a theoretical weight of (b) (4) per actuation.

## 2.4 Comments on Novel Excipients

There are no novel excipients.

## 2.5 Comments on Impurities/Degradants of Concern

The assigned CMC reviewer stated that the drug substance contained the same impurities as approved products. As such there were no concerns from a CMC perspective.

In an additional consultation, a CMC reviewer stated that the drug substance is compendial and uses the compendial limits for impurities. He further stated that in a few instances the compendial limits exceed the ICH Q3A qualification threshold (0.15%). However, they do not exceed the ICH M7 limits for mutagenic impurities of 1.5 mcg/day.

At the maximum daily dose of Fp MDPI (464 mcg/day), an impurity level (e.g., (b) (4) (b) (4)) of not more than (b) (4) % would correlate to an exposure of (b) (4) mcg/day.

(Excerpt from Sponsor's submission)

**Table 2. Impurity levels for Fluticasone propionate drug substance**

| Test                                | Analytical Procedure Reference | Source of Acceptance Criteria | Acceptance Criteria                        |
|-------------------------------------|--------------------------------|-------------------------------|--------------------------------------------|
| Organic Impurities <sup>1</sup>     | QDS0012745                     | USP monograph                 |                                            |
| (b) (4)                             |                                |                               | NMT (b) (4) %                              |
|                                     |                                |                               | NMT %                                      |
|                                     |                                |                               | NMT %                                      |
|                                     |                                |                               | NMT %                                      |
|                                     |                                |                               | NMT %                                      |
| Any individual unspecified impurity |                                |                               | NMT %                                      |
| Total impurities                    |                                |                               | NMT (b) (4) %                              |
|                                     |                                |                               | Report all impurity peaks $\geq$ (b) (4) % |

The CMC reviewer stated that there are no concerns with extractables and leachables for the drug product.

## 2.6 Proposed Clinical Population and Dosing Regimen

Fluticasone propionate MDPI is proposed for maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. (b) (4)

(b) (4) It is not indicated for the relief of acute bronchospasm.

The Sponsor has developed 3 dose strengths of Fp MDPI (i.e., low, medium, and high) for adolescent and adult patients at 55, 113, and 232 mcg BID to allow treatment of the entire spectrum of persistent asthma. The recommended starting dosages for patients aged 12 years and older are based upon the patient's asthma severity defined by their baseline ICS dose (see table below).

The maximum recommended daily dose in patients 12 years of age and older is 464 mcg per day (i.e., 232 mcg BID).

(Excerpt from Sponsor's submission)

**Table 3. Recommended Starting Dosages of Fp MDPI**

| Current Therapy                                     | Recommended Starting Dose of Fp MDPI |
|-----------------------------------------------------|--------------------------------------|
| Bronchodilators alone                               | 55 mcg bid                           |
| Inhaled corticosteroids                             |                                      |
| Low dose ( $\leq 200$ mcg Fp equivalent/day)        | 55 mcg bid                           |
| Medium dose ( $> 200$ to 500 mcg Fp equivalent/day) | 113 mcg bid                          |
| High dose ( $> 500$ to 1000 mcg Fp equivalent/day)  | 232 mcg bid                          |

Source: ISE, Section 1.5.1.1 and Section 5.2

bid=twice daily; Fp=fluticasone propionate; MDPI=multidose dry powder inhaler

The metered and delivered doses of Fp from Fp MDPI, compared with the other products used in the clinical development program, are detailed in the table below.

The proposed maximum daily dose of Fluticasone propionate (464 mcg/day) does not exceed that of the reference listed drug FLOVENT DISKUS (2000 mcg/day).

(Excerpt from Sponsor's submission)

**Table 4. Summary of metered, delivered, and nominal doses for the Fluticasone propionate MDPI relative to FLOVENT DISKUS**

| Product                     | Metered Doses Per Inhalation (mcg) | Delivered Doses Per Inhalation (mcg) | Nominal Doses Per Inhalation (mcg) | Total Daily Doses (mcg) |
|-----------------------------|------------------------------------|--------------------------------------|------------------------------------|-------------------------|
| Fp MDPI <sup>a</sup>        | 55, 113, 232                       | 51, 103, 210                         | 50, 100, 200                       | 110 to 464              |
| FLOVENT DISKUS <sup>b</sup> | 50, 100, 250                       | 46, 94, 229                          | -                                  | 200 to 2000             |
| FLOVENT HFA <sup>c</sup>    | 50, 125, 250                       | 44, 110, 220                         | -                                  | 176 to 1760             |
| FS MDPI <sup>a</sup>        | 55/14,<br>113/14,<br>232/14        | 49/12.75,<br>100/12.75,<br>202/12.75 | 50/12.5,<br>100/12.5,<br>200/12.5  | 110/28 to 464/28        |
| ADVAIR DISKUS <sup>a</sup>  | 100/50,<br>250/50,<br>500/50       | 93/45,<br>233/45,<br>465/45          | -                                  | 200/100 to 1000/100     |

Source: Fp MDPI and FS MDPI Module 3.2.P.2.2, FLOVENT DISKUS Prescribing Information 2014, FLOVENT HFA Prescribing Information 2014, and ADVAIR DISKUS Prescribing Information 2014.

<sup>a</sup> Administered as a single inhalation twice daily

<sup>b</sup> Administered as 1 to 4 inhalations twice daily

<sup>c</sup> Administered as 2 to 4 inhalations twice daily

Fp MDPI=fluticasone propionate multidose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler; HFA=hydrofluoroalkane.

Note: Delivered doses are doses delivered "under standardized in vitro test conditions."

## 2.7 Regulatory Background

A Pre-IND meeting was held with the Sponsor on July 30, 2010. It was agreed that no further preclinical testing was required as satisfactory toxicology, mutagenicity, reproductive toxicology, and carcinogenicity test results are available in previously approved product applications. However, the sponsor was requested to provide structures of impurities and degradants and any that were found to possess structural alerts for genotoxicity should be at or below acceptable qualification thresholds per the Draft Genotoxic Impurities Guidance.

Fp MDPI was developed under IND 108838 submitted on October 20, 2011.

On March 28, 2016, Teva Pharmaceuticals submitted a New Drug Application (NDA) for Fluticasone propionate pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The NDA referred to the Listed Drug, FLOVENT DISKUS, marketed under GlaxoSmithKline NDA 20,833 (approved September 29, 2000, DPARP). The proposed indication was for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older (b) (4)

It was not indicated for the relief of acute bronchospasm.

### **3 Studies Submitted**

#### **3.1 Studies Reviewed**

No nonclinical studies were submitted or required to directly support the present 505(b)(2) submission.

#### **3.3 Previous Reviews Referenced**

Pharmacology and Toxicology Reviews of IND 108838 dated November 16, 2011 and August 8, 2014

### **4 Pharmacology**

#### **4.1 Primary Pharmacology**

No primary pharmacology studies were submitted or required in the present 505(b)(2) submission.

#### **4.2 Secondary Pharmacology**

No secondary pharmacology studies were submitted or required in the present 505(b)(2) submission.

#### **4.3 Safety Pharmacology**

No safety pharmacology studies were submitted or required in the present 505(b)(2) submission.

### **5 Pharmacokinetics/ADME/Toxicokinetics**

#### **5.1 PK/ADME**

No PK/ADME studies were submitted or required in the present 505(b)(2) submission.

#### **5.2 Toxicokinetics**

No TK studies were submitted or required in the present 505(b)(2) submission.

### **6 General Toxicology**

#### **6.1 Single-Dose Toxicity**

No single-dose toxicity studies were submitted or required in the present 505(b)(2) submission.

## 6.2 Repeat-Dose Toxicity

No repeat-dose toxicity studies were submitted or required in the present 505(b)(2) submission.

## 7 Genetic Toxicology

No genetic toxicology studies were submitted or required in the present 505(b)(2) submission.

## 8 Carcinogenicity

No carcinogenicity studies were submitted or required in the present 505(b)(2) submission.

## 9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were submitted or required in the present 505(b)(2) submission.

## 10 Special Toxicology Studies

No special toxicology studies were submitted or required in the present 505(b)(2) submission.

## 11 Integrated Summary and Safety Evaluation

Teva Pharmaceuticals has submitted a 505(b)(2) NDA for Fluticasone propionate inhalation powder using a proprietary multidose dry powder inhaler (MDPI). Teva Pharmaceuticals is proposing the Fp MDPI drug product for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age or older (b) (4)

however, it is not indicated for the relief of acute bronchospasm. The product will be administered via the oral inhalation route.

The Sponsor referenced the listed drug, FLOVENT DISKUS (marketed under NDA 20,833 and utilizes the same API) to support the safety and efficacy of Fp MDPI for the proposed indication and route of administration. No nonclinical studies were conducted or required to support the safety of Fp MDPI.

There were no degradant, impurity, or extractables/leachables concerns in the drug product from a CMC perspective. In addition, the drug substance contains the same impurities as approved products.

There is a complete nonclinical program conducted with the reference product. Summaries of nonclinical reproductive toxicology studies with fluticasone propionate are provided below.

**Recommendation: The reviewer recommends approval of this 505(b)(2) NDA from the nonclinical perspective. Labeling should be modified as shown below or Section 1.3.3.**

### **Labeling Review**

For this 505(b)(2) NDA, the Sponsor provided a label for Fluticasone propionate MDPI based upon the approved product label of the listed drug, FLOVENT DISKUS. The product label for FLOVENT DISKUS was revised by DPARP in July 2015 to comply with the Pregnancy and Lactation Labeling Rule (PLLR).

The Reviewer's recommended label for Fp MDPI matches the current labeling for FLOVENT DISKUS per the PLLR conversion. In the Reviewer's recommended label below, additions are shown as underlined text and deletions are shown as strikethrough ~~text~~.

### **Fluticasone propionate MDPI**

#### **Indications and Usage in the Highlights of Prescribing Information**

Fp MDPI is a (b) (4) corticosteroid indicated:

### **8. USE IN SPECIFIC POPULATIONS**

#### **8.1 Pregnancy**

##### **Risk Summary**

(b) (4)

There are no randomized clinical (b) (4) studies (b) (4) of FP TRADENAME in pregnant women. There are clinical considerations with the use of FP TRADENAME in pregnant women [see *Clinical Considerations*]. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight, and/or skeletal variations in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mcg/m<sup>2</sup> basis [see Data]. However, fluticasone propionate administered via inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose approximately 2 times the MRHDID on a mcg/m<sup>2</sup> basis [see Data]. (b) (4)

Experience with oral corticosteroids (b) (4) suggests that rodents are more

prone to teratogenic effects from corticosteroids than humans. The estimated risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. (b) (4)

(b) (4)

### Clinical Considerations

#### *Disease-Associated Maternal and/or Embryo/Fetal Risk*

(b) (4)

In women with poorly or moderately controlled asthma, (b) (4) there is an increased risk of several perinatal adverse outcomes such as preeclampsia in the mother and prematurity, low birth weight, and small for gestational age for the neonate. Pregnant women with asthma should be closely monitored (b) (4) and (b) (4) medication adjusted as necessary to maintain optimal asthma control.

(b) (4)

### Data

### *Animal Data*

In embryofetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate was teratogenic in both species. Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, at a dose approximately 2 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat no observed adverse effect level (NOAEL) was observed at approximately 0.6 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 30 mcg/kg/day).

Cleft palate and fetal skeletal variations were observed in mouse fetuses at a dose approximately 0.5 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.16 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryofetal development study with pregnant rats dosed by the inhalation route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.5 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0.1 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal inhalation dose of 5.5 mcg/kg/day).

In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reductions of fetal body weights, in the presence of maternal toxicity at doses approximately 0.02 times the MRHDID and higher (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate for 1 fetus at a dose approximately 0.2 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was

observed in rabbit fetuses with a dose approximately 0.004 times the MRHDID (on a mcg/m<sup>2</sup> basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

(b) (4)

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

In a pre- and post-natal development study in pregnant rats dosed from late gestation through delivery and lactation (Gestation Day 17 to Postpartum Day 22), fluticasone propionate was not associated with decreases in pup body weight, and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to approximate equivalence to the MRHDID (on a mcg/m<sup>2</sup> basis with maternal subcutaneous doses up to 50 mcg/kg/day).

## 8.2 Lactation

### Risk Summary

There are no available data (b) (4) on the presence of (b) (4) fluticasone propionate in human milk, the effects on the breastfed child, or the effects on milk production, (b) (4)

Other corticosteroids have been detected in human milk. However, fluticasone propionate concentrations in plasma after inhaled therapeutic doses are low and therefore concentrations in human breast milk are likely to be correspondingly low [see Clinical Pharmacology (12.3)]. (b) (4)

-The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FP TRADENAME and any potential adverse effects on the breastfed child from (b) (4) FS TRADENAME or from the underlying maternal condition.

(b) (4)

(b) (4)

### Data

(b) (4)

#### *Animal Data*

Subcutaneous administration (b) (4) of tritiated fluticasone propionate at a dose in lactating rats approximately 0.2 times the MRHDID for adults (on a mcg/m<sup>2</sup> basis) resulted in measurable (b) (4) levels in milk.

(b) (4)

## **12. CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is 18 times that of dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results. The clinical significance of these findings is unknown.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Though effective for the treatment of asthma, corticosteroids do not affect asthma symptoms immediately. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1 to 2 weeks or

longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer.

Trials in subjects with asthma have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects with recommended doses of orally inhaled fluticasone propionate. This is explained by a combination of a relatively high local anti-inflammatory effect, negligible oral systemic bioavailability (less than 1%), and the minimal pharmacological activity of the only metabolite detected in man.

### 13. NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4) -Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 10 times the MRHDID for adults on a mcg/m<sup>2</sup> basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately equivalent to the MRHDID for adults on a mcg/m<sup>2</sup> basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the in vivo mouse micronucleus test.

(b) (4) Fertility and reproductive performance were unaffected in male and female (b) (4) rats at subcutaneous doses up to 50 mcg/kg (approximately equivalent to the MRHDID for adults on a mcg/m<sup>2</sup> basis).  
(b) (4)

**Table 5. Dosing calculations for proposed maximum clinical dose of Fluticasone propionate MDPI relative to nonclinical carcinogenicity, reproductive, fertility, teratogenicity, and overdose studies**

|                                    | Fp MDPI     |                             |               |                   |                             |          |                    |                   |
|------------------------------------|-------------|-----------------------------|---------------|-------------------|-----------------------------|----------|--------------------|-------------------|
|                                    | age         | mg/dose                     | # daily doses | mg/day            | kg                          | mg/kg    | factor             | mg/m <sup>2</sup> |
| Pediatric dose                     |             |                             |               | 0                 | 3                           | 0.00     | 25                 | 0.00              |
| Adult dose                         | >12         | 0.232                       | 2             | 0.464             | 60                          | 0.008    | 37                 | 0.286             |
|                                    | route       | mg/kg/day                   | factor        | mg/m <sup>2</sup> | Dose Ratio                  |          | Rounded Dose Ratio |                   |
|                                    |             |                             |               |                   | Adults                      | Children |                    |                   |
| <b>Carcinogenicity:</b>            |             |                             |               |                   |                             |          |                    |                   |
| mouse                              | po          | 1                           | 3             | 3                 | 10.5                        |          | 10                 | ---               |
| rat                                | po          | 0.057                       | 6             | 0.342             | 1.2                         |          | 1                  | ---               |
| rat                                | po          |                             | 6             | 0                 | 0.0                         |          | ---                | ---               |
| rat                                | po          |                             | 6             | 0                 | 0.0                         |          | ---                | ---               |
| hamster                            |             |                             | 4             | 0                 | 0.0                         |          | ---                | ---               |
| extra                              |             |                             | 20            | 0                 | 0.0                         |          | ---                | ---               |
| <b>Reproduction and Fertility:</b> |             |                             |               |                   |                             |          |                    |                   |
| mouse                              |             |                             | 3             | 0                 | 0.0                         |          | ---                | ---               |
| rat                                | sc          | 0.05                        | 6             | 0.3               | 1.0                         |          | 1                  | ---               |
| extra                              |             |                             | 20            | 0                 | 0.0                         |          | ---                | ---               |
| <b>Teratogenicity:</b>             |             |                             |               |                   |                             |          |                    |                   |
| mouse                              | sc          | 0.045                       | 3             | 0.135             | 0.5                         |          | 1/2                | ---               |
| mouse                              | sc          | 0.015                       | 3             | 0.045             | 0.2                         |          | 1/6                | ---               |
| mouse                              | po          |                             | 3             | 0                 | 0.0                         |          | ---                | ---               |
| mouse                              | sc          | 0.15                        | 6             | 0.9               | 3.1                         |          | 3                  | ---               |
| rat                                | sc          | 0.01                        | 6             | 0.06              | 0.2                         |          | 1/5                | ---               |
| rat                                | sc          | 0.1                         | 6             | 0.6               | 2.1                         |          | 2                  | ---               |
| rat                                | sc          | 0.03                        | 6             | 0.18              | 0.6                         |          | 1/2                | ---               |
| rat                                | inh         | 0.026                       | 6             | 0.156             | 0.5                         |          | 1/2                | ---               |
| rat                                | inh         | 0.006                       | 6             | 0.036             | 0.1                         |          | 1/8                | ---               |
| rabbit                             | sc          | 0.00008                     | 12            | 0.00096           | 0.0                         |          | 1/298              | ---               |
| rabbit                             | po          | 0.3                         | 12            | 3.6               | 12.6                        |          | 15                 | ---               |
| rabbit                             | sc          | 0.004                       | 12            | 0.048             | 0.2                         |          | 1/6                | ---               |
| <b>Conversion, Cor</b>             |             |                             |               |                   |                             |          |                    |                   |
| Human Age (yr)                     | Weight (kg) | Factor (kg/m <sup>2</sup> ) |               | Species           | Factor (kg/m <sup>2</sup> ) |          | Up to              | Round to nearest  |
| 0                                  | 3           | 25                          |               | dog               | 20                          |          | 1                  | 1                 |
| 0.5                                | 7           | 25                          |               | guinea pig        | 8                           |          | 10                 | 5                 |
| 1                                  | 10          | 25                          |               | hamster           | 4                           |          | 100                | 10                |
| 2                                  | 12          | 25                          |               | monkey            | 12                          |          | 1000               | 100               |
| 4                                  | 16          | 25                          |               | mouse             | 3                           |          | 10000              | 1000              |
| 6                                  | 20          | 25                          |               | rabbit            | 12                          |          |                    |                   |
| 12                                 | 50          | 37                          |               | rat               | 6                           |          |                    |                   |
| adult                              | 50          | 37                          |               |                   |                             |          |                    |                   |

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/s/  
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BRETT R JONES  
10/27/2016

TIMOTHY W ROBISON  
10/27/2016  
I concur

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number:**  
208798/208799

**Applicant:** Teva Pharmaceuticals **Stamp Date:** 03/28/2016

**Drug Name:** Fluticasone  
propionate (FP)/ FP +  
salmeterol

**NDA/BLA Type:** 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

|   | Content Parameter                                                                                                                                                                                                                                                                                                                | Yes | No | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?                                                                                                                                                      | X   |    | For the fluticasone propionate (FP) monotherapy product, the applicant is relying upon bioequivalence to the reference listed drug (RLD), FLOVENT <sup>®</sup> DISKUS (GlaxoSmithKline, NDA 020833). For the combination product, FP/salmeterol, the applicant is relying upon bioequivalence to the RLD, ADVAIR <sup>®</sup> DISKUS (GlaxoSmithKline, NDA 021077). The PharmTox information is summarized in Module 2 (0001) in both NDA's as written and tabulated summaries. No new nonclinical studies were requested or conducted to directly support the submission. Module 4 (0001) of NDA 208798 contains an extractables and leachables assessment. |
| 2 | Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?                                                                                                                                                                                                                   | X   |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 3 | Is the pharmacology/toxicology section legible so that substantive review can begin?                                                                                                                                                                                                                                             | X   |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 4 | Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?    |     |    | Not applicable. No nonclinical studies were requested or required.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 5 | If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA). |     |    | Not applicable. See Comment in #1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

|    | Content Parameter                                                                                                                                                                                                                                                                                                                                                                                                                                             | Yes | No | Comment                                                                                                                                                                                                                                                     |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6  | Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?                                                                                                                                                                                                                                              |     |    | Not applicable. See Comment in #1.                                                                                                                                                                                                                          |
| 7  | Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?                                                                                                                                                                                                                                   |     |    | Not applicable. See Comment in #1.                                                                                                                                                                                                                          |
| 8  | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?                                                                                                                                                                                                                                                                                                                                             |     |    | Not applicable, no studies were requested.                                                                                                                                                                                                                  |
| 9  | Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?                                                                                                                                                                                                                                   | X   |    | The Sponsor has provided proposed draft labeling for the monotherapy and combination products, based upon the labels of the RLDs, FLOVENT <sup>®</sup> DISKUS and ADVAIR <sup>®</sup> DISKUS, respectively. The proposed labels are in current PLLR format. |
| 10 | Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)                                                                                                                                                                                                                                                                                                                                    | X   |    | The PharmTox reviewer will consult with the CMC reviewer regarding any impurity issues.                                                                                                                                                                     |
| 11 | If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?                                                                                                                                                                                                                                                                                                                                                                   |     |    | Not applicable.                                                                                                                                                                                                                                             |
| 12 | If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)? | X   |    | These are 505(b)(2) applications (see comment in #1). Bridging for both applications was based upon clinical bioequivalence.                                                                                                                                |

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes\_\_\_\_\_**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

None

## **PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

APPEARS THIS WAY ON ORIGINAL

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/s/  
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BRETT R JONES  
05/13/2016

TIMOTHY W ROBISON  
05/13/2016  
I concur