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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

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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

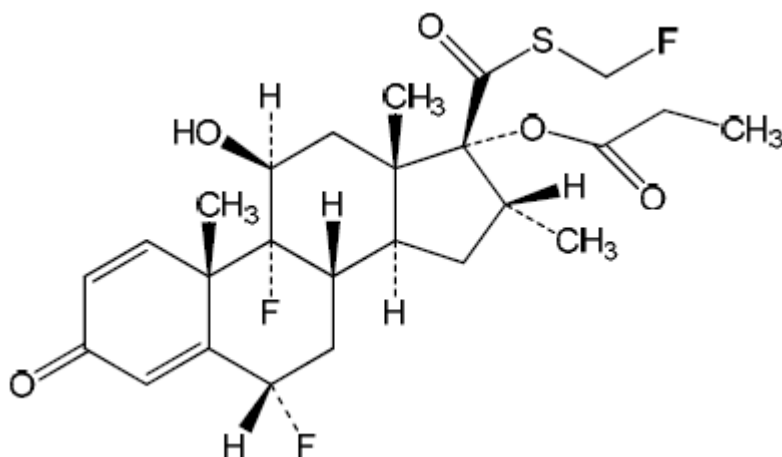
Molecular Formula/Molecular Weight

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

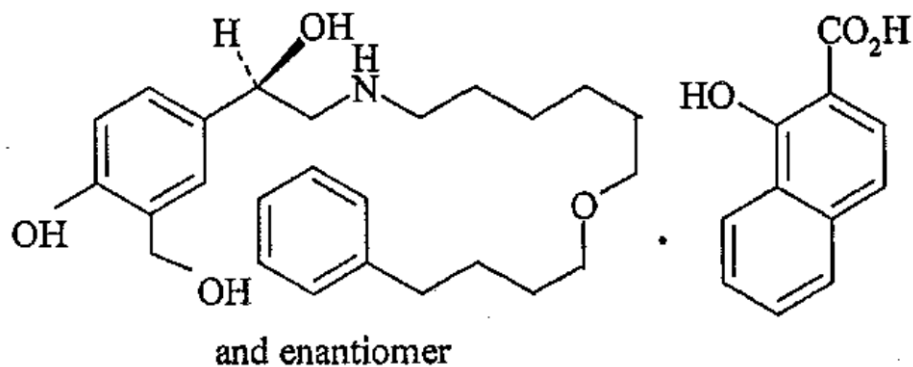
Salmeterol xinafoate: $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$ / 603.8

Structure or Biochemical Description

Fluticasone propionate:



Salmeterol xinafoate:

**Pharmacologic Class**

Fluticasone propionate: Corticosteroid

Salmeterol xinafoate: Long acting β_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[®] Diskus[®]

NDA 21433: GSK, Flovent[®] 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 ^a		
	55 mcg	113 mcg	232 mcg
Fluticasone propionate, (b) (4)	51 mcg	103 mcg	210 mcg
Lactose monohydrate	(b) (4)		

^a 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 ^a	113/14 mcg ^a	232/14 mcg ^a
Fluticasone propionate, (b) (4)	49 mcg	100 mcg	202 mcg
Salmeterol xinafoate, (b) (4)	18.52 mcg ^b	18.52 mcg ^b	18.52 mcg ^b
Lactose monohydrate	(b) (4)		

^a This is based on a theoretical weight of (b) (4) per actuation^b 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.

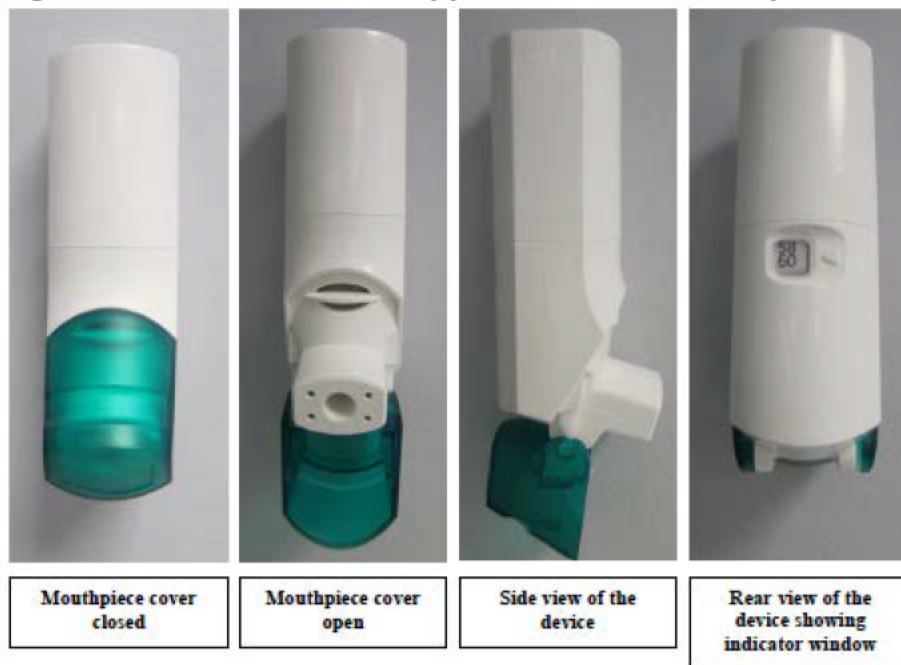
2.5 Comments on Extractables and Leachables Studies

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 (Continuous contact with drug formulation)	(b) (4)		Reservoir to store powder
			Lid to contain powder in reservoir
			Receives metered dose
Class 2 (Transient contact with drug formulation)	(b) (4)		
Class 3 (Transient contact with drug formulation and patient mucosa)			
Class 4 (Contact with patient mucosa)			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 ^A (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)

^AExposures (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
≥ 2 < 10 microns	< (b) (4) counts
≥ 10 < 25 microns	< (b) (4) counts
≥ 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 ≤ 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 15 or 18 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

Title
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.¹

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,

¹ 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)	(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 ≤ 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:

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

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

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

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

The current Environment Protection Agency (EPA) standards (24 hr averaging time) for PM-2.5 (particulate matter ≤ 2.5 mcm) and PM-10 (particulate matter ≤ 10 mcm) are 25 mcg/m³ and 50 mcg/m³, respectively. Therefore, an EPA acceptable daily mass (mcg) of particulate matter for a human respiratory volume of $\frac{4}{3} \pi (9 \text{ mcm})^3$ (i.e., 2 actuations/day) would be approximately $\frac{4}{3} \pi (9 \text{ mcm})^3$ mcg/day and $\frac{4}{3} \pi (9 \text{ mcm})^3$ mcg/day based on PM-2.5 and PM-10 standards, respectively.

The maximum proposed daily mass of foreign particulates (≤ 10 mcm) from the FS and FP MDPI products at $\frac{4}{3} \pi (9 \text{ mcm})^3$ 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/

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 208,799
Supporting document/s:	SDN#1
Applicant's letter date:	March 29, 2016
CDER stamp date:	March 29, 2016
Product:	Fluticasone propionate/salmeterol xinafoate inhalation powder (FS MDPI)
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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APPEARS THIS WAY ON ORIGINAL

1 Executive Summary

1.1 Introduction

Fluticasone propionate/Salmeterol xinafoate (FS) oral inhalation powder is an approved drug product indicated for the treatment of asthma in patients aged 4 years and older. It is currently marketed in the U.S. as ADVAIR DISKUS (DPARP; Approval Action on August 24, 2000). The Sponsor submitted the present 505(b)(2) application to support the development of Fluticasone propionate/Salmeterol xinafoate inhalation powder using a proprietary multidose dry powder inhaler (MDPI). The FS MDPI contains the same active ingredients as ADVAIR DISKUS, which is marketed at strengths of 100/50, 250/50, and 500/50 mcg BID, and is the reference drug.

1.2 Brief Discussion of Nonclinical Findings

The Sponsor refers to the Reference Listed Drug, ADVAIR DISKUS, marketed under NDA 21,077, which utilizes the same APIs and is approved for the treatment of asthma in patients aged 4 years and older via the oral inhalation route. For this submission, the Sponsor is proposing the FS MDPI as a fixed dose combination product containing a corticosteroid and a long-acting β -agonist (LABA) for the treatment of asthma in patients aged 12 years and older. It is not indicated for the relief of acute bronchospasm.

There are complete nonclinical programs for the individual monoproducts, Fluticasone propionate and Salmeterol xinafoate, as well as the combination. No new nonclinical pharmacology or toxicology studies were conducted or required to directly support the safety of Fluticasone propionate or Salmeterol xinafoate for the current 505(b)(2) submission.

Based upon the Agency's previous findings of safety and efficacy for the reference listed drug, ADVAIR DISKUS, and the public literature, there is sufficient information from the nonclinical perspective to recommend the approval of NDA 208,799.

1.3 Recommendations

1.3.1 Approvability

NDA 208,799 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 FS MDPI (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 FS MDPI label.

Fluticasone propionate/Salmeterol xinafoate MDPI

HIGHLIGHTS OF PRESCRIBING INFORMATION **INDICATIONS AND USAGE**

FS TRADENAME (b) (4) is a fixed dose combination product containing a corticosteroid and a LABA indicated for:

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of (b) (4) FS TRADENAME or individual monoproducts, fluticasone propionate and salmeterol xinafoate, in pregnant women. There are clinical considerations with the use of FS TRADENAME in pregnant women [see Clinical Considerations]. (b) (4)

Animal reproduction studies are available with the combination of fluticasone propionate and salmeterol xinafoate as well as individual monoproducts. 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/m² 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 less than the MRHDID on a mcg/m² basis [see Data]. Experience with oral corticosteroids (b) (4)

(b) (4) suggests that rodents- (b) (4) are more prone to teratogenic effects from corticosteroids than humans. Oral administration of salmeterol to pregnant rabbits caused teratogenicity characteristic of beta-adrenoceptor stimulation at maternal doses approximately 700 times the MRHDID on a mcg/m² basis. These adverse effects generally occurred at large multiples of the MRHDID when salmeterol was administered by the oral route to achieve high systemic exposures. No such effects occurred at an oral salmeterol dose approximately 420 times the MRHDID [see Data]. (b) (4)

(b) (4)

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)

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 (b) (4) in the neonate. (b) (4) Pregnant women with asthma should be closely monitored (b) (4) and medication adjusted as necessary to maintain optimal asthma control.

(b) (4)

(b) (4)

Data

(b) (4)

Animal Data

Fluticasone Propionate and Salmeterol:

(b) (4)

(b) (4)

(b) (4)

In an embryofetal development study with pregnant rats that

received the combination of subcutaneous administration of fluticasone propionate and oral administration of salmeterol at doses of 0/1000, 30/0, 10/100, 30/1000, and 100/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) during the period of organogenesis, findings were generally consistent with the individual monoproducts and there was no exacerbation of expected fetal effects. Omphalocele, increased embryofetal deaths, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, when combining fluticasone propionate at a dose approximately 2 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 100 mcg/kg/day) and a dose of salmeterol at approximately 3500 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg/day). The rat no observed adverse effect level (NOAEL) was observed when combining fluticasone propionate at a dose 0.6 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 30 mcg/kg/day) and a dose of salmeterol at approximately 350 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 1000 mcg/kg/day).

In an embryofetal development study with pregnant mice that received the combination of subcutaneous administration of fluticasone propionate and oral administration of salmeterol at doses of 0/1400, 40/0, 10/200, 40/1400, or 150/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) during the period of organogenesis, findings were generally consistent with the individual monoproducts and there was no exacerbation of expected fetal effects. Cleft palate, fetal death, increased implantation loss, and delayed ossification were observed in mouse fetuses when combining fluticasone propionate at a dose approximately 1.4 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 150 mcg/kg/day) and salmeterol at a dose approximately 1470 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg/day). No developmental toxicity was observed at combination doses of fluticasone propionate up to approximately 0.8 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 40 mcg/kg) and doses of salmeterol up to approximately 420 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 1400 mcg/kg).

Fluticasone Propionate:

(b) (4)

(b) (4)

(b) (4)

-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/m² basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat NOAEL was observed at approximately 0.6 times the MRHDID (on a mcg/m² 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/m² 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/m² 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/m² 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/m² basis with a maternal inhalation dose of 5.5 mcg/kg/day).

(b) (4)

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/m² 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/m² 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/m² basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

In a pre- and post-natal development study in pregnant rats dosed by the subcutaneous route 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/m² basis with maternal subcutaneous doses up to 50 mcg/kg/day).

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

Salmeterol:-

(b) (4)

(b) (4)

In three embryofetal development studies, pregnant rabbits received oral administration of salmeterol at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. In pregnant Dutch rabbits administered salmeterol doses approximately 70 times the MRHDID (on a mcg/m² basis at maternal oral doses of 1000 mcg/kg/day

and higher), fetal toxic effects were observed characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at a salmeterol dose approximately 420^{(b) (4)} times the MRHDID (on a mcg/m² basis at a maternal oral dose of 600^{(b) (4)} mcg/kg/day). New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at a salmeterol dose approximately 7000^{(b) (4)} times the MRHDID (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg/day).

In two embryofetal development studies, pregnant rats received salmeterol by oral administration at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. Salmeterol produced no maternal toxicity or embryofetal effects at doses up to 3500 times the MRHDID (on a mcg/m² basis at maternal oral doses up to 10,000 mcg/kg/day).

In a peri-and post-natal development study in pregnant rats dosed by the oral route from late gestation through delivery and lactation, salmeterol at a dose 3500 times the MRHDID (on mcg/m² basis with a maternal oral dose of 10,000 mcg/kg/day) was fetotoxic and decreased the fertility of survivors.

Salmeterol xinafoate crossed the placenta following oral administration to mice and rats.

8.2 Lactation

Risk Summary

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

ther corticosteroids^{(b) (4)}
have been detected in human milk.

However, fluticasone propionate and salmeterol 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)*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FS TRADENAME and any potential adverse effects on the breastfed child from^{(b) (4)}
-FS TRADENAME or from the underlying maternal condition.

(b) (4)

Data

(b) (4)

Animal Data

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

(b) (4) Oral administration of salmeterol at a dose in lactating rats approximately 2900 times the MRHDID for adults (on a mcg/m² basis) resulted in measurable levels in milk.

(b) (4)

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

FS TRADENAME: FS TRADENAME contains both fluticasone propionate and salmeterol. The mechanisms of action described below for the individual components apply to FS TRADENAME. These drugs represent 2 different classes of medications (a synthetic corticosteroid and a LABA) that have different effects on clinical, physiologic, and inflammatory indices.

Fluticasone Propionate

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.

Salmeterol Xinafoate

Salmeterol is a selective LABA. In vitro studies show salmeterol to be at least 50 times more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor– induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone propionate:

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 10 times the MRHDID on a mcg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately equivalent to the MRHDID on a mcg/m² 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 micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately equivalent to the MRHDID for adults on a mcg/m² basis).

Salmeterol: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1-400 mcg/kg and above (approximately 24^{(b)(4)} times the MRHDID on a mcg/m² basis) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at 200^{(b)(4)} mcg/kg (approximately 35 times the MRHDID on a mcg/m² basis).

In a 24-month oral and inhalation carcinogenicity study in Sprague-Dawley rats, salmeterol caused a dose related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 680^{(b)(4)} mcg/kg and above (approximately 240 times the MRHDID on a mcg/m² basis). No tumors were seen at 210^{(b)(4)} mcg/kg (approximately 7^{(b)(4)} times the MRHDID on a mcg/m² basis). These findings in rodents are similar to those reported previously for other beta adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. ^{(b)(4)}

(b) (4)

Fertility and reproductive performance were unaffected in male and female rats at oral doses up to 2000 mcg/kg (approximately 690^{(b)(4)} times the MRHDID for adults on a mcg/m² basis).

13.2 Animal Toxicology and Pharmacology

Preclinical: Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical relevance of these findings is unknown.

2 Drug Information

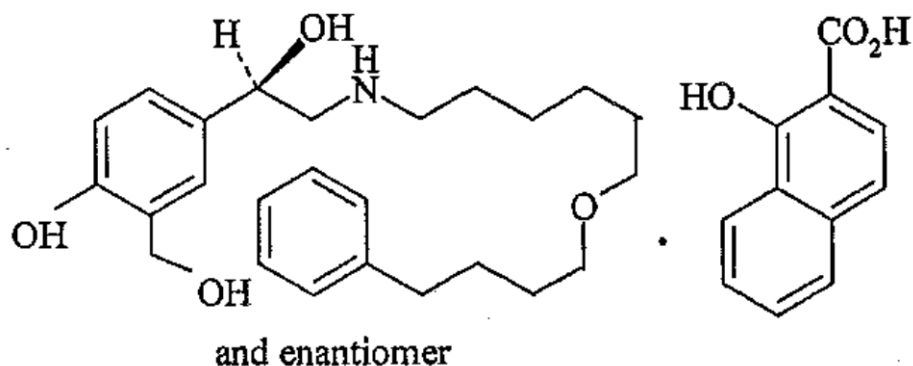
2.1 Drug

Tradename

FS TRADENAME

Generic Name

Fluticasone propionate/Salmeterol xinafoate

Chemical Name4-hydroxy- α' -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthene carboxylate**Molecular Formula/Molecular Weight** $C_{25}H_{37}NO_4$. $C_{11}H_8O_3$ / 603.8**Structure or Biochemical Description****Pharmacologic Class**Long acting β_2 -agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 208798:

IND 072240: Teva, Fluticasone propionate/salmeterol xinafoate

NDA 21077: GSK, ADVAIR DISKUS

2.3 Drug Formulation

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. The products are formulated in three strengths, which meter 55/14, 113/14, or 232/14 mcg of fluticasone propionate/salmeterol xinafoate, respectively, from the mouthpiece 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 FS MDPI products

Ingredient	55/14 mcg ^a	113/14 mcg ^a	232/14 mcg ^a
Fluticasone propionate, (b) (4)	49 mcg	100 mcg	202 mcg
Salmeterol xinafoate, (b) (4)	18.52 mcg ^b	18.52 mcg ^b	18.52 mcg ^b
Lactose monohydrate	(b) (4)		

^a This is based on a theoretical weight of (b) (4) per actuation

^b 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.

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 (see below).

At the maximum daily dose of FS MDPI (464/28 mcg/day), an impurity level of not more than (b) (4) % would correlate to an exposure of (b) (4) mcg/day (e.g., Related Compounds (b) (4) and (b) (4) mcg/day (b) (4) impurity) for the fluticasone propionate and salmeterol xinafoate drug substances, respectively.

(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 ¹	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 ≥ (b) (4) %

(Excerpt from Sponsor's submission)

Table 3. Impurity levels for Salmeterol xinafoate drug substance

i.	(b) (4)	Not more than	(b) (4) %
ii.		Not more than	%
iii.		Not more than	%
iv.		Not more than	%
v.		Not more than	%
vi.		Not more than	%
vii.		Not more than	%
viii. Any unspecified impurity		Not more than	0%
ix. Total unspecified impurities		Not more than	%
x. Total impurities		Not more than	%

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

2.6 Proposed Clinical Population and Dosing Regimen

Fluticasone propionate/salmeterol xinafoate MDPI is proposed for the treatment of asthma in patients aged 12 years and older. It is not indicated for the relief of acute bronchospasm.

The Sponsor has developed 3 dose strengths of FS MDPI (i.e., low, medium, and high) for adolescent and adult patients at 55/14, 113/14, and 232/14 mcg BID. The recommended starting dosages for patients aged 12 years and older are based upon the patient's asthma severity (see table below).

The maximum recommended daily dose in patients 12 years of age and older is 464/28 mcg per day (i.e., 232/14 mcg BID).

(Excerpt from Sponsor's submission)

Table 4. Recommended Starting Dosages of FS MDPI

Current Therapy	FS TRADENAME Recommended Starting Dose
Inhaled corticosteroids (with or without long-acting beta agonists)	
• Low (≤ 200 mcg FP* equivalent /day)	55/14 mcg BID
• Medium (greater than 200-500 mcg FP equivalent/day)	113/14 mcg BID
• High (greater than 500-1000 mcg FP equivalent/day)	232/14 mcg BID

* FP denotes fluticasone propionate

The metered and delivered doses of Fluticasone propionate and salmeterol xinafoate in FS MDPI, compared with the other products used in the clinical development program, are detailed in the table below.

The proposed maximum daily doses of Fluticasone propionate (464 mcg/day) and Salmeterol xinafoate (28 mcg/day) do not exceed that of the reference listed drug ADVAIR DISKUS (1000 and 100 mcg/day, respectively).

(Excerpt from Sponsor's submission)

Table 5. Summary of metered, delivered, and nominal doses for the FS MDPI relative to ADVAIR DISKUS

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

^a Administered as a single inhalation twice daily

^b Administered as 1 to 4 inhalations twice daily

^c 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 Meetings were held with the Sponsor on December 5, 2005, March 25, 2008, and December 1, 2009. During the December 1, 2009 meeting, 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.

The FS MDPI was developed under IND 72240 submitted on October 31, 2012.

On March 28, 2016, Teva Pharmaceuticals submitted a New Drug Application (NDA) for Fluticasone propionate/salmeterol xinafoate pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The NDA referred to the Listed Drug, ADVAIR DISKUS, marketed under GlaxoSmithKline NDA 21,077 (approved August 24, 2000, DPARP). The proposed indication was for the treatment of asthma in patients aged 12 years and older. 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.

3.2 Studies Not Reviewed



The nonclinical sections of the FS MDPI products proposed label are based on the approved ADVAIR DISKUS product label.

3.3 Previous Reviews Referenced

Pharmacology and Toxicology Review of IND 72240 dated November 21, 2012.

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/Salmeterol xinafoate (FS) inhalation powder using a proprietary multidose dry powder inhaler (MDPI). Teva Pharmaceuticals is proposing the FS MDPI drug product for the treatment of asthma in patients aged 12 years and older. 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, ADVAIR DISKUS (marketed under NDA 21,077 and utilizes the same APIs) to support the safety and efficacy of FS MDPI for the proposed indication and route of administration. ADVAIR DISKUS is approved for the treatment of asthma in patients aged 4 years and older. No nonclinical studies were conducted or required to directly support the safety of FS 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 are complete nonclinical programs for the individual and combined inhaled product use of fluticasone propionate and salmeterol xinafoate.

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/Salmeterol xinafoate MDPI

(b) (4)

Presented below is the Applicant's proposed wording for the FS TRADENAME product insert. Also presented below are the nonclinical revisions to the Applicant's proposed labeling and a rationale for the proposed changes. The Reviewer's recommended label for FS MDPI generally follows the currently approved labeling for ADVAIR DISKUS, although Sections 8.1 and 8.2 were updated to comply with the PLLR.

Fluticasone propionate/Salmeterol xinafoate MDPI

Applicant's Proposed Labeling for Indications and Usage and Use in Specific Populations in the Highlights of Prescribing Information Section:

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

FS TRADENAME (b) (4) is a fixed dose combination product containing a corticosteroid and a LABA indicated for:

DPARP's Proposed Nonclinical Labeling for Indications and Usage and Use in Specific Populations in the Highlights of Prescribing Information:

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

FS TRADENAME (b) (4) is a fixed dose combination product containing a corticosteroid and a LABA indicated for:

Rationale for Changes in Indications and Usage and Use in Specific Populations in the Highlights of Prescribing Information:

No changes.

Applicant's Proposed Labeling for Sections 8.1 and 8.2:

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

(b) (4)

(b) (4)

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

(b) (4)

(b) (4)

(b) (4)



Data

(b) (4)



Animal Data

Fluticasone Propionate and Salmeterol:

(b) (4)

(b) (4)



(b) (4)



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

(b) (4)



8.2 Lactation

Risk Summary

(b) (4)

[Redacted text block]

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FS TRADENAME and any potential adverse effects on the breastfed child from fluticasone propionate and salmeterol xinafoate or from the underlying maternal condition.

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

Data

(b) (4)

[Redacted text block]

Animal Data

(b) (4)

[Redacted text block]

DPARP's Proposed Nonclinical Labeling for Sections 8.1 and 8.2:

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of FS TRADENAME or individual monoproducts, fluticasone propionate and salmeterol xinafoate, in pregnant women. There are clinical considerations with the use of FS TRADENAME in pregnant women [see *Clinical Considerations*]. Animal reproduction studies are available with the combination of fluticasone propionate and salmeterol xinafoate as well as individual monoproducts. 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/m² 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 less than the MRHDID on a mcg/m² basis [see *Data*]. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. Oral administration of salmeterol to pregnant rabbits caused teratogenicity characteristic of beta-adrenoceptor stimulation at maternal doses approximately 700 times the MRHDID on a mcg/m² basis. These adverse effects generally occurred at large multiples of the MRHDID when salmeterol was administered by the oral route to achieve high systemic exposures. No such effects occurred at an oral salmeterol dose approximately 420 times the MRHDID [see *Data*].

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.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

In women with poorly or moderately controlled asthma, 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 in the neonate. Pregnant

women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control.

Data

Animal Data

Fluticasone Propionate and Salmeterol: In an embryofetal development study with pregnant rats that received the combination of subcutaneous administration of fluticasone propionate and oral administration of salmeterol at doses of 0/1000, 30/0, 10/100, 30/1000, and 100/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) during the period of organogenesis, findings were generally consistent with the individual monoproducts and there was no exacerbation of expected fetal effects. Omphalocele, increased embryofetal deaths, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, when combining fluticasone propionate at a dose approximately 2 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 100 mcg/kg/day) and a dose of salmeterol at approximately 3500 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg/day). The rat no observed adverse effect level (NOAEL) was observed when combining fluticasone propionate at a dose 0.6 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 30 mcg/kg/day) and a dose of salmeterol at approximately 350 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 1000 mcg/kg/day).

In an embryofetal development study with pregnant mice that received the combination of subcutaneous administration of fluticasone propionate and oral administration of salmeterol at doses of 0/1400, 40/0, 10/200, 40/1400, or 150/10,000 mcg/kg/day (as fluticasone propionate/salmeterol) during the period of organogenesis, findings were generally consistent with the individual monoproducts and there was no exacerbation of expected fetal effects. Cleft palate, fetal death, increased implantation loss, and delayed ossification were observed in mouse fetuses when combining fluticasone propionate at a dose approximately 1.4 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 150 mcg/kg/day) and salmeterol at a dose approximately 1470 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg/day). No developmental toxicity was observed at combination doses of fluticasone propionate up to approximately 0.8 times the MRHDID (on a mcg/m² basis at a maternal subcutaneous dose of 40 mcg/kg) and doses of salmeterol up to approximately 420 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 1400 mcg/kg).

Fluticasone Propionate: 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/m² basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat NOAEL was observed at approximately 0.6 times the MRHDID (on a mcg/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

In a pre- and post-natal development study in pregnant rats dosed by the subcutaneous route 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/m² basis with maternal subcutaneous doses up to 50 mcg/kg/day).

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

Salmeterol: In three embryofetal development studies, pregnant rabbits received oral administration of salmeterol at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. In pregnant Dutch rabbits administered salmeterol doses approximately 700 times the MRHDID (on a mcg/m² basis at maternal oral doses of 1000 mcg/kg/day and higher), fetal toxic effects were observed characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at a salmeterol dose approximately 420 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 600 mcg/kg/day). New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at a salmeterol dose approximately 7000 times the MRHDID (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg/day).

In two embryofetal development studies, pregnant rats received salmeterol by oral administration at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. Salmeterol produced no maternal toxicity or embryofetal effects at doses up to 3500 times the MRHDID (on a mcg/m² basis at maternal oral doses up to 10,000 mcg/kg/day).

In a peri- and post-natal development study in pregnant rats dosed by the oral route from late gestation through delivery and lactation, salmeterol at a dose 3500 times the MRHDID (on mcg/m² basis with a maternal oral dose of 10,000 mcg/kg/day) was fetotoxic and decreased the fertility of survivors.

Salmeterol xinafoate crossed the placenta following oral administration to mice and rats.

8.2 Lactation

Risk Summary

There are no available data on the presence of fluticasone propionate or salmeterol in human milk, the effects on the breastfed child, or the effects on milk production. Other corticosteroids have been detected in human milk. However, fluticasone propionate and salmeterol 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)]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FS TRADENAME and any potential adverse effects on the breastfed child from FS TRADENAME or from the underlying maternal condition.

Data

Animal Data

Subcutaneous administration of tritiated fluticasone propionate at a dose in lactating rats approximately 0.2 times the MRHDID for adults (on a mcg/m² basis) resulted in measurable levels in milk. Oral administration of salmeterol at a dose in lactating rats approximately 2900 times the MRHDID for adults (on a mcg/m² basis) resulted in measurable levels in milk.

Rationale for Changes in Sections 8.1 and 8.2:

(b) (4)

Sections 8.1 and 8.2 of the proposed FS TRADENAME label were modified to comply with the PLLR by rearrangement of the information in the most recently approved ADVAIR DISKUS product label and incorporation of information from the product label for FLOVENT DISKUS, which was recently converted to comply with the PLLR.

The Risk Summary reports that there are no randomized clinical studies of the combination of fluticasone propionate and salmeterol xinafoate or individual

monoproducts in pregnant women. Adverse findings from animal reproductive toxicity studies with fluticasone propionate and/or salmeterol xinafoate are reported. It is noted that experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. Adverse effects with salmeterol generally occurred at large multiples of the MRHDID when salmeterol was administered by the oral route to achieve high systemic exposures.

Details about the period of drug administration and adverse findings from embryofetal development studies with the combination of fluticasone propionate and salmeterol xinafoate or individual monoproducts in mice, rats, and rabbits are described. Data from an ePPND study in pregnant rats dosed subcutaneously with fluticasone propionate was added. Data from an ePPND study in pregnant rats dosed orally with salmeterol xinafoate was added. Doses in animals and corresponding ratios relative to the MRHDID for FS TRADENAME were uniformly revised in the label to mcg/kg/day and mcg/m², respectively.

Additional language is proposed for the Risk Summary in Section 8.2 to highlight that fluticasone propionate and salmeterol xinafoate concentrations in plasma after inhaled therapeutic doses are low and therefore concentrations in human breast milk are likely to be correspondingly low. Additional language for the Animal Data in Section 8.2 was added that oral administration of salmeterol xinafoate in lactating rats (i.e., ~2900 times the MRHDID in adults on a mcg/m² basis) resulted in measurable levels in milk.

(b) (4)

Applicants Proposed Labeling for Section 12.1:

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

FS TRADENAME: FS TRADENAME contains both fluticasone propionate and salmeterol. The mechanisms of action described below for the individual components apply to FS TRADENAME. These drugs represent 2 different classes of medications (a synthetic corticosteroid and a LABA) that have different effects on clinical, physiologic, and inflammatory indices.

Fluticasone Propionate

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.

Salmeterol Xinafoate

Salmeterol is a selective LABA. In vitro studies show salmeterol to be at least 50 times more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor– induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

DPARP's Proposed Nonclinical Labeling for Section 12.1:

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

FS TRADENAME: FS TRADENAME contains both fluticasone propionate and salmeterol. The mechanisms of action described below for the individual components apply to FS TRADENAME. These drugs represent 2 different classes of medications (a synthetic corticosteroid and a LABA) that have different effects on clinical, physiologic, and inflammatory indices.

Fluticasone Propionate

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.

Salmeterol Xinafoate

Salmeterol is a selective LABA. In vitro studies show salmeterol to be at least 50 times more selective for beta2-adrenoceptors than albuterol. Although beta2-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1-adrenoceptors are the predominant receptors in the heart, there are also beta2-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective beta2-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor–induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

Rationale for Changes in Section 12.1:

No changes. The Sponsor is seeking approval for the use of FS TRADENAME in the treatment of asthma. The paragraph in Section 12.1 of the product label for ADVAIR DISKUS regarding its use for the treatment of COPD is not part of the present label.

Applicants Proposed Labeling for Section 13.1 and 13.2:**13. NONCLINICAL TOXICOLOGY****13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**Fluticasone propionate:

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 10 times the MRHDID on a mg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately equivalent to the MRHDID on a mg/m² 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 micronucleus test.

Salmeterol:

In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 24^{(b)(4)} times the MRHDID on a mg/m² basis) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at 0.2 mg/kg (approximately 35 times the MRHDID on a mg/m² basis).

In a 24-month oral and inhalation carcinogenicity study in Sprague-Dawley rats, salmeterol caused a dose related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 240 times the MRHDID on a mg/m² basis). No tumors were seen at 0.21 mg/kg (approximately 7^{(b)(4)} times the MRHDID on a mg/m² basis). These findings in rodents are similar to those reported previously for other beta adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. ^{(b)(4)}

[REDACTED]

13.2 Animal Toxicology and/or Pharmacology

Preclinical: Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical relevance of these findings is unknown.

DPARP's Proposed Nonclinical Labeling for Sections 13.1 and 13.2:**13. NONCLINICAL TOXICOLOGY****13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**Fluticasone propionate:

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 10 times the MRHDID on a mcg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately equivalent to the MRHDID on a mcg/m² 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 micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately equivalent to the MRHDID for adults on a mcg/m² basis).

Salmeterol: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1400 mcg/kg and above (approximately 240 times the MRHDID on a mcg/m² basis) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at 200 mcg/kg (approximately 35 times the MRHDID on a mcg/m² basis).

In a 24-month oral and inhalation carcinogenicity study in Sprague-Dawley rats, salmeterol caused a dose related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 680 mcg/kg and above (approximately 240 times the MRHDID on a mcg/m² basis). No tumors were seen at 210 mcg/kg (approximately 75 times the MRHDID on a mcg/m² basis). These findings in rodents are similar to those reported previously for other beta adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at oral doses up to 2000 mcg/kg (approximately 690 times the MRHDID for adults on a mcg/m² basis).

13.2 Animal Toxicology and Pharmacology

Preclinical: Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic

evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical relevance of these findings is unknown.

Rationale for Changes in Sections 13.1 and 13.2:

A paragraph was added in Section 13.1 regarding fertility and reproductive performance in rats dosed subcutaneously with fluticasone propionate as the Sponsor had neglected to include it in the product label. The paragraph in Section 13.1 regarding fertility and reproductive performance in rats dosed orally with salmeterol xinafoate was updated. Dosage values and corresponding ratios relative to the MRHDID for FS TRADENAME were uniformly revised in Section 13.1 to mcg/kg/day and mcg/m², respectively.

Table 6. Dosing calculations for proposed maximum clinical dose of Fluticasone propionate in FS and Fp MDPI relative to nonclinical carcinogenicity, reproductive, fertility, teratogenicity, and overdosage studies

	Fp MDPI							
	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m ²
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 ²	Dose Ratio		Rounded Dose Ratio	
					Adults	Children		
Carcinogenicity:								
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		---	---
Reproduction and Fertility:								
mouse			3	0	0.0		---	---
rat	sc	0.05	6	0.3	1.0		1	---
extra			20	0	0.0		---	---
Teratogenicity:								
mouse	sc	0.045	3	0.135	0.5		1/2	---
mouse	sc	0.01	3	0.03	0.1		1/10	---
mouse	sc	0.04	3	0.12	0.4		1/2	---
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	0.0006	12	0.0072	0.0		1/40	---
rabbit	sc	0.00008	12	0.00096	0.0		1/298	---
rabbit	sc	0.004	12	0.048	0.2		1/6	---
Conversion, Cor								
Human Age (yr)	Weight (kg)	Factor (kg/m ²)		Species	Factor (kg/m ²)		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						

Table 7. Dosing calculations for proposed maximum clinical dose of Salmeterol xinafoate in FS MDPI relative to nonclinical carcinogenicity, reproductive, fertility, teratogenicity, and overdose studies

Drug:		FS MDPI - Salmeterol						
	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m ²
Pediatric			2	0	3	0.00	25	0.00
Adult	>12	0.014	2	0.028	60	0.00	37	0.02
	route	mg/kg/d	conv. factor	mg/m ²	Dose Ratio		Rounded Dose Ratio	
					Adults	Children	Adults	Children
<u>Carcinogenicity:</u>								
mouse		1.4	3	4.2	243.24	---	240	---
mouse		0.2	3	0.6	34.75	---	35	---
rat		0.68	6	4.08	236.29	---	240	---
rat		0.21	6	1.26	72.97	---	75	---
<u>Reproduction and Fertility:</u>								
mouse		0.2	3	0.6	34.75	N/A	35	N/A
rat	po	2	6	12	694.98	N/A	690	N/A
rat			6	0	---	N/A	---	N/A
extra			#N/A	#N/A	---	N/A	---	N/A
<u>Teratogenicity:</u>								
mouse	po	10	3	30	1737.45	N/A	1700	N/A
rat	po	10	6	60	3474.90	N/A	3500	N/A
rat	po	1	6	6	347.49	N/A	350	N/A
rabbit	po	1	12	12	694.98	N/A	690	N/A
rabbit	po	10	12	120	6949.81	N/A	6900	N/A
rabbit	po	0.6	12	7.2	416.99	N/A	420	N/A
extra			#N/A	#N/A	---	N/A	---	N/A
Conversion, Correction, and Rounding Factors:								
Human Age (yr)	Weight (kg)	Factor (kg/m ²)		Species	Factor (kg/m ²)	Exposure greater than x-times human		Round to nearest
0	3	25		dog	20		1	1
1	10	25		guinea pig	8		10	5
2	12	25		hamster	4		100	10
4	16	25		monkey	12		1000	100
6	20	25		mouse	3		10000	1000
12	50	37		rabbit	12			
				rat	6			

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/s/

BRETT R JONES
11/04/2016

TIMOTHY W ROBISON
11/04/2016
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 [®] DISKUS (GlaxoSmithKline, NDA 020833). For the combination product, FP/salmeterol, the applicant is relying upon bioequivalence to the RLD, ADVAIR [®] 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 ² 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, (b) (4) 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

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

/s/

BRETT R JONES
05/13/2016

TIMOTHY W ROBISON
05/13/2016
I concur