CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208799Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 208799
Review 1

Drug Name/Dosage Form	Fluticasone Proprionate and Salmeterol Xinafoate Inhalation Powder for Multidose Dry Powder Inhaler
Strength	55/14mcg; 113/14mcg; 232/14 mcg, 60 actuations each
Route of Administration	Oral Inhalation
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceuticals
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	**Ben Stevens**	**OPQ/ONDP/DNDPAPI/BII**
Drug Product	**Xiaobin Shen**	**OPQ/ONDP/DNDPII/BIV**
Process	**Joanne Wang**	**OPQ/OPF/DPAIII/BVIII**
Microbiology	**None**	**OPQ/OPF/DMA/BIII**
Facility	**Christina Daniel-Capacci**	**OPQ/OPF/DIA/BII**
Biopharmaceutics		**OPQ/ONDP/DB/BII**
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	**Julia Pinto**	**OPQ/ONDP/DNDPII/BIV**
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)	**Xiaobin Shen**	**OPQ/ONDP/DNDPII/BIV**

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

B. DMF#	Type	Holder	Item Referenced	Status	Date Review completed	Comments
15745	II	Teva	Fluticasone Proprionate	1	2016	N/A
(b) (4)	II	(b) (4)		1	2016	N/A
	IV			4	N/A	N/A

Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS: NONE

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH	Complete	CDRH OC recommends approval		Crystal Lewis/ Juandria Williams
Clinical				
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

The drug product is combination product comprising fluticasone propionate and salmeterol inhalation powder dispensed in a multi-dose dry powder inhaler [FS MDPI]). It is manufactured in three strengths with each MDPI designed to deliver a minimum of 60 actuations. Each actuation represents one therapeutic dose of the product, used to treat asthma. The combination product is compounded with Lactose Monohydrate as the only excipient. Both APIs are USP grade and supported by DMFs 15745 (b) (4) for fluticasone and salmeterol respectively. The MDPI device is a multi-component device with a reservoir (b) (4) to hold the drug-lactose drug product blend. Each drug product device is sealed (b) (4) inside an aluminum pouch. All data provided to support the quality and manufacture of the drug products is satisfactory and supports an expiry of 21 months, 19 months and 22 months for the 55/14mcg; 113/14mcg; 232/14 mcg strengths respectively. All Facilities are recommended as adequate, by the Office of Compliance and Office of Process and Facilities. Therefore this NDA is recommended for approval.

II. Summary of Quality Assessments

A. Product Overview

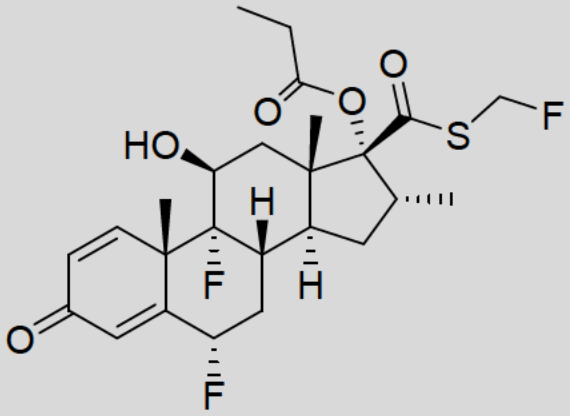
Drug Substance

The active ingredients in the drug product are fluticasone propionate and salmeterol xinafoate. The manufacture and quality data to support both APIs is referenced to DMF 15745 (b) (4) respectively. Each has been reviewed and deemed adequate for use in the preparation of the drug product, by Ben Stevens, Ph.D. Sufficient stability data is provided in the respective DMFs to support a retest period of (b) (4) months for Fluticasone Proprionate and (b) (4) months for Salmeterol Xinafoate.

Chemical Name and Structure: Taken from B. Stevens review the Drug substances.

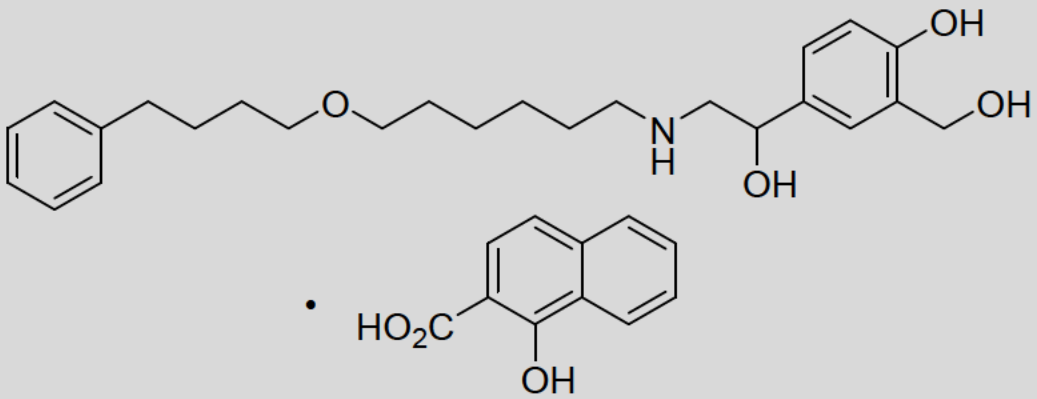
Fluticasone propionate (USAN), fluticasone (BAN/INN), (b) (4)

(2) S-Fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate (Chemical Names).



Chemical Name and Structure: Salmeterol xinafoate (USAN), (b) (4)

(2) (±)-4-Hydroxy-α[1]-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-*m*-xylene-α,α′-diol 1-hydroxy-2-naphthoate (salt) (Chemical Names).



Drug Product

B. The drug product is fluticasone propionate/salmeterol inhalation powder (or fluticasone propionate/salmeterol multi-dose dry powder inhaler [FS MDPI]). It is manufactured in three strengths. The device is designed to deliver a minimum of 60 actuations. Each actuation represents one therapeutic dose for the product. The

only excipient is lactose monohydrate which is widely used in the preparation of dry powder inhalation products. Three batches of drug product were manufactured at commercial scale of (b)(4)kg. Release and stability data support the manufacturing process and controls. An expiry of 21 months, 19 months and 22 months for the 55/14mcg; 113/14mcg; 232/14 mcg strengths respectively, is granted.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

This NDA is recommended for approval.

Application Technical Lead Signature:

Julia C. Pinto, Ph.D.
Branch Chief(Acting)
ONDP/Division II/Branch IV

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(b) (4)

R Regional Information

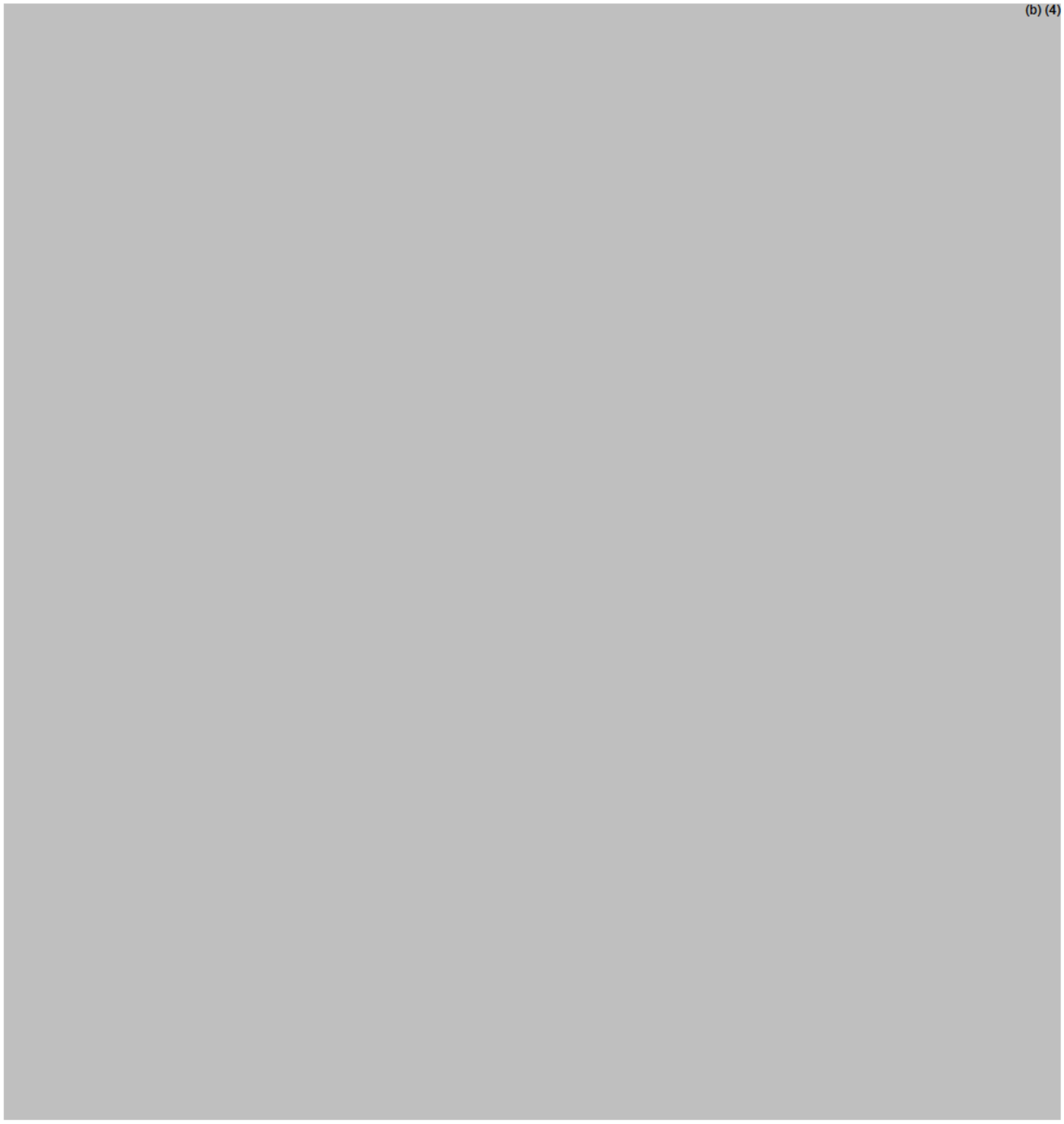
1.14 Labeling

Immediate Container Label

The labels are reproduced below for all strengths. The labels are organized as commercial product front label, back label, and sample front label, back label.

Start of Sponsor Material

(b) (4)



(b) (4)

End of Sponsor Material

Reviewer's Assessment: Acceptable after the editorial revision identified below.

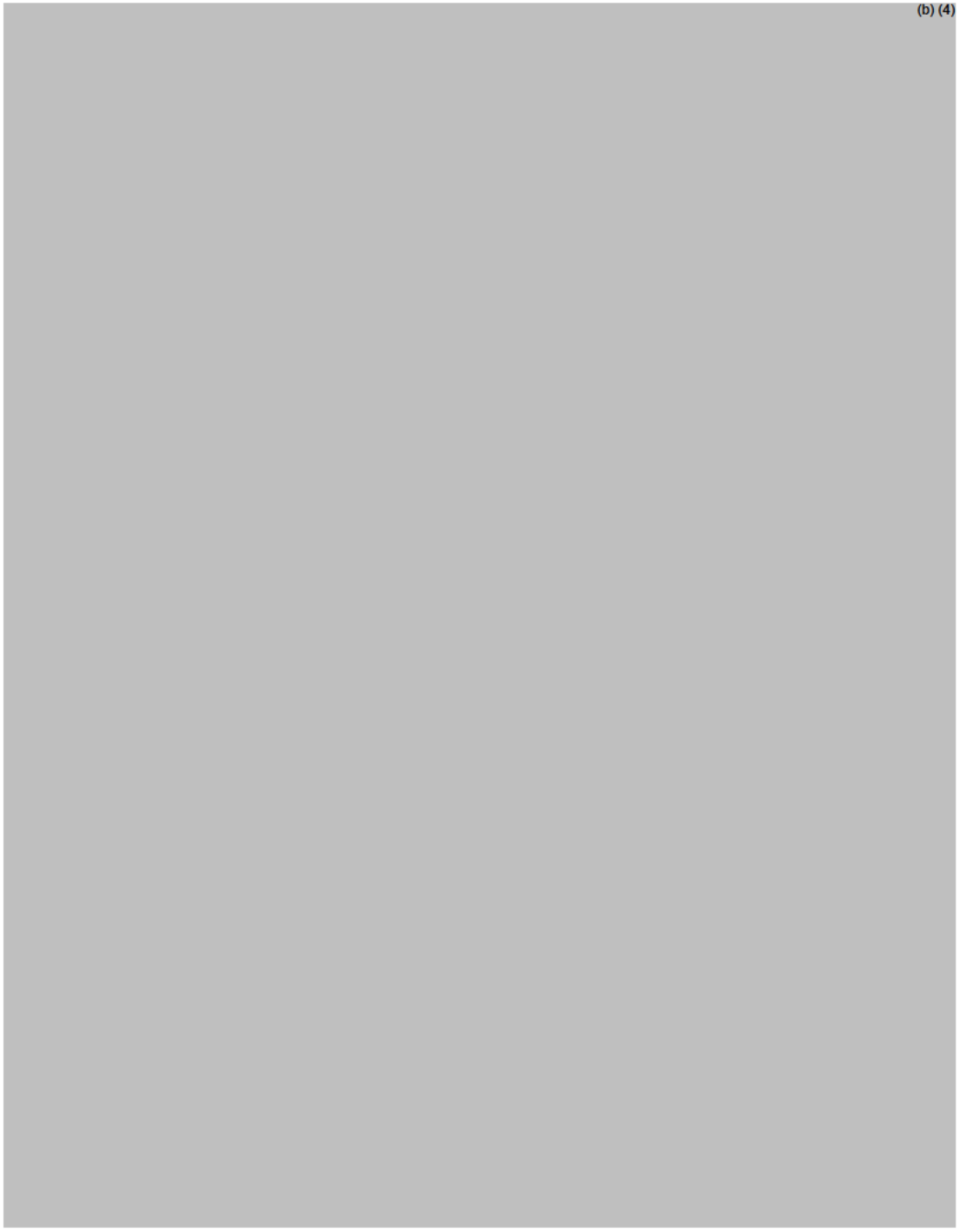
The label contains all required information, except that the lot number and expiration date do not seem to have space to be printed. Note that 21 CFR 201.10(i) requires the lot number to be included in small labels.

Pouch Labeling

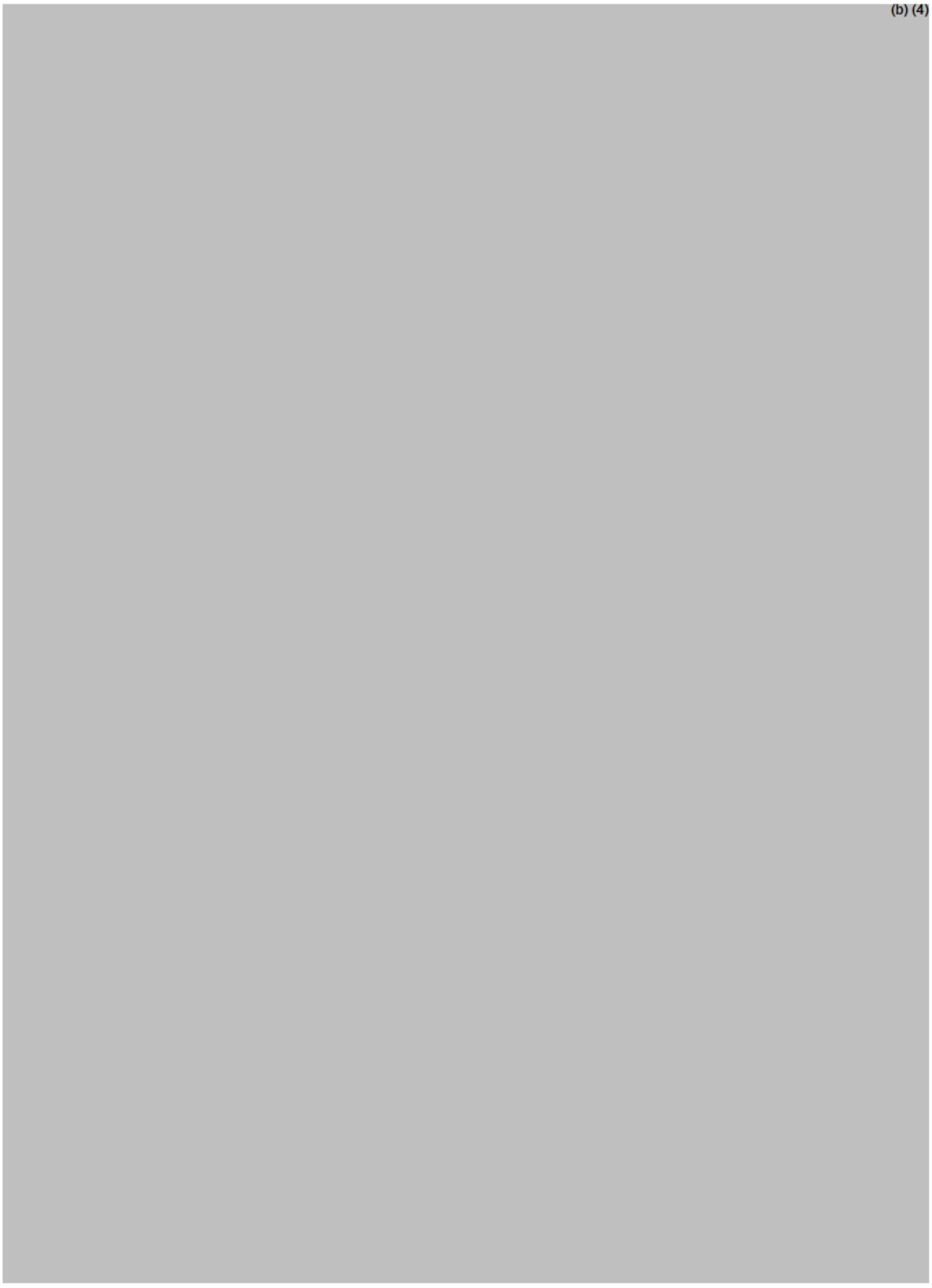
The pouch labels are reproduced below for all strengths. The pouch labels are organized as commercial product label and sample label.

Start of Sponsor Material

(b) (4)



(b) (4)



(b) (4)

End of Sponsor Material

Reviewer's Assessment: Acceptable after the editorial revision identified below.

The label contains all required information, except (as marked above) that the salt equivalent statement (b) (4) ***. The correct statement should be "14 mcg of salmeterol base, equivalent to 20.3 mcg of salmeterol xinafoate".***

Carton Labeling

The carton labels are reproduced below for all strengths. The labels are organized as commercial product carton and sample product carton.

Start of Sponsor Material

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6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

The label contains all required information, except (as marked above) that the salt equivalent statement (b) (4). The correct statement should be "14 mcg of salmeterol base, equivalent to 20.3 mcg of salmeterol xinafoate".

Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Start of Sponsor Material

DOSAGE FORMS AND STRENGTHS

Inhalation Powder (b) (4)

fluticasone propionate (55 mcg, 113 mcg, or 232 mcg) and salmeterol (14 mcg) (b) (4)

(b) (4)

End of Sponsor Material

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Pending Established Name: Fluticasone propionate, Salmeterol Xinafoate	Acceptable. Note that the final drug product proprietary name has not been updated yet in the package insert.
Dosage form, route of administration	Dosage: Inhalation Powder Route: Oral Inhalation	Acceptable Acceptable
Controlled drug substance symbol (if applicable)	NA	Acceptable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	See above in the reproduced highlights section.	Acceptable

Conclusion: Acceptable. The correct proprietary name will be updated before an approval action is taken.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Inhalation Powder	Acceptable
Strengths: in metric system	Meters 55 mcg, 113 mcg, or 232 mcg of fluticasone propionate with 14 mcg of salmeterol from the device reservoir and delivers 49, 100, or 202 mcg of fluticasone propionate with 12.75 mcg of salmeterol, respectively, from the mouthpiece per actuation.	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	A multidose, inhalation-driven, dry powder inhaler for oral inhalation. (b) (4) . FS TRADENAME is supplied as a white dry powder inhaler with a yellow cap in a sealed foil pouch with desiccant.	Acceptable

Conclusion: Acceptable.

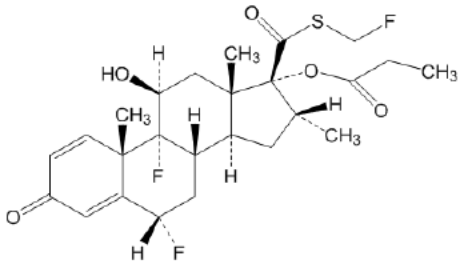
#11: Description (21CFR 201.57(c)(12))

Start of Sponsor Material

11 DESCRIPTION

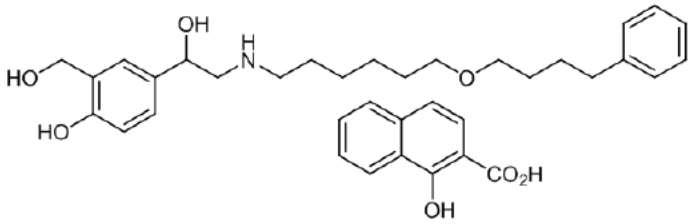
FS TRADENAME 55/14 mcg, FS TRADENAME 113/14 mcg and FS TRADENAME 232/14 mcg are combinations of fluticasone propionate and salmeterol xinafoate.

One active component of FS TRADENAME is fluticasone propionate, a corticosteroid having the chemical name *S*-(fluoromethyl) 6α,9-difluoro-11ß,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17ß-carbothioate, 17-propionate, and the following chemical structure:



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

The other active component of FS TRADENAME is salmeterol xinafoate, a $beta_2$–adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. It has the chemical name 4-hydroxy-α-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate and the following chemical structure:



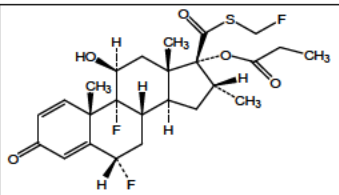
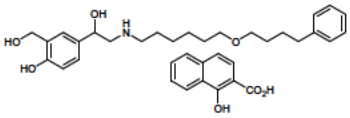
Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

FS TRADENAME is a white multidose dry powder inhaler for oral inhalation only. It contains a formulation blend of fluticasone propionate, salmeterol xinafoate, and lactose monohydrate (which may contain milk proteins). The opening of the mouthpiece cover meters 5.5 mg of the formulation from the device reservoir, which contains 55 mcg, 113 mcg, or 232 mcg of fluticasone propionate, and 14 mcg of salmeterol base, equivalent to 20.3 mcg of salmeterol xinafoate. Patient inhalation through the mouthpiece causes the deagglomeration and aerosolization of the drug particles as the formulation moves through the cyclone component of the device. This is followed by dispersion into the airstream.

Under standardized in vitro test conditions, the FS TRADENAME inhaler delivers 49, 100, or 202 mcg of fluticasone propionate and 12.75 mcg of salmeterol base, equivalent to x mcg of salmeterol xinafoate, with lactose from the mouthpiece.

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

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary: To be updated. Established Name: Fluticasone propionate and salmeterol xinafoate inhalation powder.	Acceptable. Note that the final proprietary name has not been updated yet in the package insert. Acceptable
Dosage form and route of administration	Dosage form: Inhalation powder Route of administration: Oral	Acceptable Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	55 mcg, 113 mcg, or 232 mcg of fluticasone propionate, and 14 mcg of salmeterol base, equivalent to 20.3 mcg of salmeterol xinafoate.	Acceptable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Lactose monohydrate.	Acceptable
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Fluticasone propionate is a corticosteroid Salmeterol xinafoate is a beta2–adrenergic bronchodilator.	Acceptable
Chemical name, structural formula, molecular weight	Fluticasone propionate: S-(fluoromethyl) 6α,9-difluoro-11ß,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17ß-carbothioate, 17-propionate	Acceptable Acceptable Acceptable

	 MW is 500.6. Salmeterol xinafoate: 1 hydroxy 2 naphthoic acid salt of salmeterol. It has the chemical name 4-hydroxy-α -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate  MW is 603.8.	
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	N/A	N/A

Conclusion: Acceptable

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Start of Sponsor Material

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FS TRADENAME is supplied in the following three strengths as a white dry-powder inhaler. Each inhaler has a (b) (4) cap and is packaged individually in a foil pouch in a carton. Each inhaler contains 0.45g of the formulation and provides 60 actuations:

STRENGTH	NDC CODE
FS TRADENAME 55/14 mcg	NDC 59310-805-06
FS TRADENAME 113/14 mcg	NDC 59310-812-06
FS TRADENAME 232/14 mcg	NDC 59310-822-06

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

16.2 Storage and Handling

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

Keep out of reach of children.

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

End of Sponsor Material

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	FS TRADENAME 55/14 mcg FS TRADENAME 113/14 mcg FS TRADENAME 232/14 mcg	Acceptable
Available units (e.g., bottles of 100 tablets)	60 actuations per unit.	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	A while dry-powder inhaler individually packaged in a foil pouch in a carton. The NDC numbers are provided for the three commercial strengths.	Acceptable
Special handling (e.g., protect from light, do not freeze)	N/A	N/A
Storage conditions	Store at room temperature (between 15°C and 25°C (59°C and 77°F); excursions permitted between 15°-30°C (59°-86°F).	Acceptable

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Teva Pharmaceutical Industries Ltd. Jerusalem, Israel	Acceptable

Conclusion: Acceptable.

Post-Approval Commitments

Pending.

Reviewer's Assessment: Pending the applicant's responses to the Agency's information request.

Lifecycle Management Considerations

Pending.

QUALITY ASSESSMENT

Reviewer's Assessment: Pending the applicant's responses to the Agency's information request.

List of Deficiencies

1. Clarify the location on the drug product immediate container (MDPI device) label where the drug product lot number and expiry will be printed.
2. The salt equivalent statement you included for salmeterol xinafoate on the pouch label and carton (b) (4). Correct it to state as "14 mcg of salmeterol base, equivalent to 20.3 mcg of salmeterol xinafoate".

Primary Drug Product Reviewer Name and Date: Xiaobin Shen, 17-Nov-2016.

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Julia Pinto, 17-Nov-2016

Julia Pinto

Digitally signed by Julia Pinto
Date: 11/18/2016 09:07 36AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

Xiaobin Shen

Digitally signed by Xiaobin Shen
Date: 11/17/2016 09:31 32PM
GUID: 508da71f00029eecfb90bd87e5a608ab

DRUG PRODUCT

– Chemistry Review 01 Addendum –

This review addendum evaluates the applicant responses to the Agency's information requests and the Pharmaceutical Development section of the NDA not previously evaluated in the main review.

As shown below, all responses are acceptable. The overall recommendation remains as approval.

Responses to Information Request

Amendment 0022 Submitted on 17-Nov-2016

Information Request 1 –

Provide an analysis of your proposed specifications for Foreign Particulate Matter (FPM) from a safety point of view. We note that the acceptance criteria are 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.

Applicant Response Summary –

The applicant provided an analysis of the proposed specifications from a safety point of view. Briefly, the analysis calculated that even at the currently proposed specification limit, the worst case scenario exposure to the foreign particulates in mass would be at a maximum of (b) (4) mcg/day, which is much lower than the current EPA standard of approximately 1008 mcg/day and 4320 mcg/day for the $PM_{2.5}$ and PM_{10} respectively, and is also lower than the current WHO standard of approximately 720 mcg/day and 1440 mcg/day for the $PM_{2.5}$ and PM_{10} respectively. Such exposure therefore is considered acceptable based on the drug product's daily dose.

Despite of the safety justifications, Teva commits to re-assess the acceptance criteria of the foreign particulate matter after testing ten commercial batches per product strength.

Reviewer's Assessment: Acceptable.

The provided safety justification and plan to revisit the specifications are reasonable.

Information Request 2 –

Provide the results of an investigation into the observation that there was a significant increase in FPM on stability for the fluticasone propionate product while there was a slight increase for

the fluticasone propionate/salmeterol xinafoate during storage. We note that both products use the same device and same excipient.

Applicant Response Summary –

Both the fluticasone propionate (Fp) product and the fluticasone propionate/salmeterol xinafoate (FS) product use the same device and excipient. However, the two differ in the weight of the formulation delivered per actuation. Each emitted actuation from the Fp product has a mass of (b) (4) mcg while each emitted actuation from the FS product has a mass of (b) (4) mcg. When the FPM results are plotted on a per unit weight per actuation basis, to account for the difference in emitted mass, there is no difference in the stability trends for FPM between the Fp and FS products.

Reviewer's Assessment: Acceptable.

The provided analysis and justification are reasonable.

Amendment 0023 Submitted on 18-Nov-2016

Information Request 1 –

The validation data showed that Method QDP0102666 quantifies all fluticasone propionate related substances consistently low, reaching a mean of (b) (4) % for Impurity (b) (4) and (b) (4) % for Impurity (b) (4) Such under estimation likely also exists for other related substances. Apply a correction factor to the impurity calculations.

Applicant Response Summary –

Teva agrees to update the related substances method with a correction factor of (b) (4) to account for the low fluticasone propionate recoveries reported in the validation report. This correction factor takes into consideration the lowest recovery observed in the validation data and will ensure no impurities are under reported. Teva commits to submit the updated methods to the Agency by 12/9/16.

Reviewer's Assessment: Acceptable.

Information Request 2 –

(b) (4)

Applicant Response Summary –

(b) (4)

Reviewer's Assessment: Acceptable.

Information Request 3 –

(b) (4)

Applicant Response Summary –

(b) (4)

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(b) (4)

[redacted]

Information Request 4 –

The up to (b) (4) months of controlled room temperature (CRT) stability data do not support the following acceptance limits of the drug product for NDA 208799 for fluticasone propionate and salmeterol xinafoate inhalation powder:

- *salmeterol assay acceptance limit of (b) (4) %,*
- *the specified fluticasone propionate impurity acceptance limits of NMT (b) (4) %,*
- *the fluticasone propionate total impurity acceptance limit of NMT (b) (4) %,*
- *the Salmeterol (b) (4) impurity acceptance limit of NMT (b) (4) %*
- *and the total salmeterol xinafoate impurity acceptance limit of NMT (b) (4) %.*

Tighten the corresponding acceptance limits to be more reflective of the CRT stability data.

Applicant Response Summary –

Teva agrees to tighten the acceptance limits to be more reflective of the submitted CRT stability data. The revised specifications are listed in Table 3. Teva commits to submit updated specifications to the Agency by 12/9/16.

Table 3: Proposed Changes to the Acceptance Limits of the Drug Product for NDA 208799

Parameter	Current Specification	Revised Specification
Salmeterol Xinafoate Assay	Salmeterol Xinafoate (as base): (b) (4) %w/w	Salmeterol Xinafoate (as base): (b) (4) %w/w[a]
Specified Fluticasone Propionate Impurities	(b) (4) NMT (b) (4) % NMT (b) (4) %	(b) (4) NMT (b) (4) % NMT (b) (4) %
Total Fluticasone Propionate Impurities	Total Impurities: NMT (b) (4) %	Total Impurities: NMT (b) (4) %
Salmeterol Xinafoate (b) (4)	(b) (4) NMT (b) (4) %	(b) (4) NMT (b) (4) %
Total Salmeterol Xinafoate Impurities	Total Impurities: NMT (b) (4) %	Total Impurities: NMT (b) (4) %

(b) (4) %w/w corresponds to (b) (4) % of the target at (b) (4) %w/w

Reviewer's Assessment: Acceptable.

The revised acceptance limits are acceptably reflective of the assay and stability data.

Reviewer's Assessment: Noted. The development findings and results support the provided quality control of the DMPI drug product.

Post-Approval Commitments

Not applicable.

Reviewer's Assessment: There is no post-approval commitment.

Lifecycle Management Considerations

None.

Reviewer's Assessment: Not applicable.

Final Drug Product Specifications –

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Table 1: Specifications for Finished Products

Analytical Procedure	Method	Acceptance Criteria
Appearance and Description	QDP0033470	
Appearance of inhaler		An inhaler with (b) (4) yellow mouthpiece cover (complies with standard) Absence of visual damage or powder leakage.
Dose Counter		The numeral 60 is visible in the dose counter window.
Appearance of powder by visual inspection		White (b) (4) powder.
Appearance of powder by UV-Vis		Reflectance is ≥ (b) (4)%.
Identification by UPLC[a]	QDP0033473	Retention times of the principle peaks in the sample chromatogram are within (b) (4)% of the corresponding retention times of the drug peaks in the standard chromatogram.
Identification by TLC[a]	QDP0033474	The Retention Factor (R_F) of the principle spots in the sample must correspond to those obtained for the fluticasone propionate and salmeterol xinafoate (as base) standards.
Strength: 55/14 mcg		
Assay (drug content per inhaler)	QDP0033473	Fluticasone Propionate: (b) (4) %w/w[b] Salmeterol Xinafoate (as base): (b) (4) %w/w[c]

Analytical Procedure	Method	Acceptance Criteria
Strength: 113/14 mcg		
Assay (drug content per inhaler)	QDP0033473	Fluticasone Propionate: (b) (4) %w/w[d] Salmeterol Xinafoate (as base): (b) (4) %w/w[c]
Strength: 232/14 mcg		
Assay (drug content per inhaler)	QDP0033473	Fluticasone Propionate: (b) (4) %w/w[e] Salmeterol Xinafoate (as base): (b) (4) %w/w[c]
Related Substances	QDP0102666	Fluticasone Propionate: (b) (4) NMT (b) (4) % NMT % Any individual unspecified impurity: NMT (b) (4) % Total impurities: NMT (b) (4) % Salmeterol Xinafoate (as base): (b) (4) NMT (b) (4) % NMT % Salmeterol (b) (4): NMT (b) (4) % Any individual unspecified impurity: NMT (b) (4) % Total impurities: NMT (b) (4) %
(b) (4)		
Net Content (Fill Weight) [a]	QDP0033473	(b) (4) g

Analytical Procedure	Method	Acceptance Criteria
Dose Content Uniformity	QDP0102664	The label claim emitted dose (LCED) for fluticasone propionate/salmeterol is 49 mcg/12.75 mcg , 100 mcg/12.75 mcg or 202 mcg/12.75 mcg Tier 1 (n = 10 inhalers) Collect one actuation per inhaler at the beginning of inhaler life. The amount of fluticasone propionate and salmeterol (free base) should comply with: a. NMT (b) (4) of 10 determinations is outside (b) (4) (b) (4)% of the LCED. b. All individual determinations are within (b) (4)% to (b) (4)% of the LCED. The mean of all determinations is within (b) (4)% of the LCED. Tier 2 decision: a. If (b) (4) determinations are outside the limit of (b) (4)%, and NMT (b) is outside (b) (4)%, but none are outside (b) (4)% of the LCED, and b. The mean of all determinations is within (b) (4) (b) (4)% of the LCED, Test an additional 20 inhalers. Tier 2 (n = 20 inhalers) a. NMT (b) (4) of 30 determinations are outside (b) (4) (b) (4)% of the LCED. b. NMT (b) (4) of 30 determinations is outside (b) (4) (b) (4)% and none are outside (b) (4)% of the LCED. c. The mean of all determinations is within (b) (4) (b) (4)% of the LCED.

Analytical Procedure	Method	Acceptance Criteria
Dose Content Uniformity through Inhaler life	QDP0102664	The label claim emitted dose (LCED) for fluticasone propionate/salmeterol is 49 mcg/12.75 mcg , 100 mcg/12.75 mcg or 202 mcg/12.75 mcg Tier 1 (n = 3 inhalers) Collect one actuation per inhaler at the beginning, middle and end of inhaler life. The amount of fluticasone propionate and salmeterol (free base) should comply with: a. NMT (b) (4) of 9 determinations is outside (b) (4) % of the LCED. b. All individual determinations are within (b) (4) % to (b) (4) % of the LCED. c. The mean of all determinations at each stage of inhaler life is within (b) (4) % of the LCED. Tier 2 decision: a. If (b) (4) determinations are outside the limit of (b) (4) %, and NMT (b) (4) is outside (b) (4) %, but none are outside (b) (4) % of the LCED, and b. The mean of all determinations is within (b) (4) (b) (4) % of the LCED, Test an additional 6 inhalers each at each stage of inhaler life. Tier 2 (n = 6 inhalers) a. NMT (b) (4) of 27 determinations are outside (b) (4) (b) (4) % of the LCED. b. NMT (b) (4) of 27 determinations is outside (b) (4) (b) (4) % and none are outside (b) (4) % of the LCED. c. The means of all determinations at each stage of inhaler life are within (b) (4) % of the LCED.
Number of Actuations per inhaler	QDP0032148	NLT 60 Actuations
Dose Counter Reading	QDP0032148	(b) (4)

Analytical Procedure	Method	Acceptance Criteria
Strength: 55/14 mcg		
Aerodynamic Particle Size Distribution (APSD) by (b) (4)	(b) (4)	For n=5 inhalers perform determinations on each inhaler at beginning and end of inhaler life. Fluticasone Propionate (b) (4) Salmeterol (as base) (b) (4)
Strength: 113/14 mcg		

Analytical Procedure	Method	Acceptance Criteria
Aerodynamic Particle Size Distribution (APSD) by (b) (4)	QDP0100589	For n=5 inhalers perform determinations on each inhaler at beginning and end of inhaler life. Fluticasone Propionate (b) (4) Salmeterol (as base) (b) (4)

Analytical Procedure	Method	Acceptance Criteria
Strength: 232/14 mcg		
Aerodynamic Particle Size Distribution (APSD) by (b) (4)	QDP0100589	For n=5 inhalers perform determinations on each inhaler at beginning and end of inhaler life. Fluticasone Propionate (b) (4) Salmeterol (as base) (b) (4)
Foreign Particulate Matter	QDP0095709	≥ 2 µm and < 10 µm ≤ (b) (4) ≥ 10 µm and < 25 µm ≤ ≥ 25 µm ≤
Microbiological Examination for Non-Sterile Products	QDP0042121	Total aerobic microbial count (TAMC): NMT (b) (4) CFU/g Total combined yeasts and moulds count (TYMC): NMT (b) (4) CFU/g *Pseudomonas aeruginosa*: Absent/g *Staphylococcus aureus*: Absent/g Bile-tolerant Gram negative bacteria: Absent/g

[a] For Release Only
[b] (b) (4) % w/w corresponds to (b) (4) % of the target at (b) (4) %w/w.
[c] % w/w corresponds to % of the target at %w/w.
[d] %w/w corresponds to % of the target at %w/w.
[e] %w/w corresponds to % of the target at %w/w.

Julia Pinto

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Xiaobin Shen

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PROCESS

NDA: 208799

Drug Product Name / Strength: AirDuo RespiClick, Fluticasone Propionate and Salmeterol Xinafoate, 55/14 mcg, 113/14 mcg, 232/14 mcg Inhalation Powder

Route of Administration: Oral Inhalation

Applicant Name: Teva Pharmacerutical Industries Ltd.

Review Summary:

The application is APPROVABLE from a process perspective. This is a drug-device combination product. The proposed manufacturing process involves four main unit operations: (b) (4) The proposed commercial process and manufacturing site are same as that used for the registration batches. (b) (4) The process risk was high since there were two APIs in the blend, and the drug loadings were both extremely low. Yield of the registration batches were low because applicant (b) (4) Critical process parameters proposed for commercial batches were supported by registration batch data. The proposed in-process controls are adequate and acceptance criteria well justified. The process description provides clear instructions for manufacturing

List Submissions being reviewed (table):

Document(s) Reviewed	Date Received
NDA Original Application	03/29/2016
Response to FDA Request for Information – CMC (13Oct2016)	10/28/2016
Response to FDA Request for Information – CMC (28Oct2016)	11/16/2016

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

P.3 Manufacture

Batch Formula

Table 1: Batch Formula of Fluticasone Propionate/Salmeterol Inhalation Powder 55/14, 113/14, and 232/14 mcg, 60 Actuation Products for a Batch Size of (b) (4) Inhalers

Ingredient	Quality Standard	Quantity (g)		
		55/14 mcg	113/14 mcg	232/14 mcg
Fluticasone propionate, (b) (4)	USP	(b) (4)		
Salmeterol xinafoate (b) (4)	USP			
Lactose monohydrate	USP/NF			
Total (g)				

Table 2: Batch Overages for Fluticasone Propionate and Salmeterol Xinafoate

Ingredient	Quality Standard	Quantity					
		55/14 mcg		113/14 mcg		232/14 mcg	
		Weight (g)	Percentage (%)*	Weight (g)	Percentage (%)*	Weight (g)	Percentage (%)*
Fluticasone propionate	USP	(b) (4)					
Salmeterol Xinafoate	USP						

*percentage of overage (b) (4)

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

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

Product Strength	Product Batch Number	Use of Batch	Certificate of Analysis	Reference Number
55/14 mcg	FS2004	Clinical and Registration	COA - Finished Product FS MDPI 55/14 (Lot FS2004)	QDP0101064
	FS2005	Registration	COA - Finished Product FS MDPI 55/14 (Lot FS2005)	QDP0101065
	FS2006	Registration	COA - Finished Product FS MDPI 55/14 (Lot FS2006)	QDP0101066
113/14 mcg	FS4006	Clinical and registration	COA - Finished Product FS MDPI 113/14 (Lot FS4006)	QDP0101067
	FS4007	Clinical and registration	COA - Finished Product FS MDPI 113/14 (Lot FS4007)	QDP0101068
	FS4008	Registration	COA - Finished Product FS MDPI 113/14 (Lot FS4008)	QDP0101070
232/14 mcg	FS6006	Clinical and registration	COA - Finished Product FS MDPI 232/14 (Lot FS6006)	QDP0101071
	FS6007	Registration	COA - Finished Product FS MDPI 232/14 (Lot FS6007)	QDP0101072
	FS6008	Registration	COA - Finished Product FS MDPI 232/14 (Lot FS6008)	QDP0101086

Note: Executed Batch Records FS2005, FS4006, FS6006 are provided in 3.2.R

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

Secondary Reviewer Name and Date:

Derek S. Smith, Ph.D. – 16 Dec 2016

Derek Smith

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Date: 12/16/2016 04:53 22PM
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Christina Capacci-Daniel

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Date: 12/16/2016 03:32 28PM
GUID: 51dc71a50000c6c3f0b616578caafab6

Julia Pinto

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Date: 1/19/2017 04:21:51PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

NDA-208799-ORIG-1 » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Edit Task | Task Actions

Task Summary | Task Details | Documents | Approvals | Updates | Application Life Cycle

Inspection Management Form

As of Jan 10, 2017 5:07 pm GMT

Assigned To

Christina Capacci Daniel

Edit Assignment

This was done on
Dec 15, 2016
(26 days ago)

Status
Complete

This task is waiting on
Facilities

Last Update	Submitted On
Dec 15, 2016	Mar 30, 2016

Reference Number
7229933

Inspection Management Form

NDA-208799-ORIG-1

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility

Facility DUNS Number: (b) (4)
Action Indicated Status: Compliant

District Office Recommendation:
District Office Recommendation Reasons:
District Office Decision Factors:

Office of Process and Facilities Recommendation: Approve Facility
Office of Process and Facilities Recommendation Reasons: Based on File Review

(b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility

(b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility

(b) (4) TEVA PHARMACEUTICALS INDUSTRIES LIMITED | 3003414719 | (b) (4) | Approve Facility

TEVA PHARMACEUTICALS INDUSTRIES LIMITED | 3003414719 | QID ORALLY INHALED DELIVERY | Approve Facility

(b) (4)

TEVA PHARMACEUTICAL INDUSTRIES LIMITED | 3005202697 | CTL CONTROL TESTING LABORATORY | Approve Facility

(b) (4) EXC EXCIPIENT (ALSO KNOWN AS INACTIVE

(b) (4) MIS NOT ELSEWHERE CLASSIFIED |

Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

Submission Manufacturing Facilities

Facility Status	Completion Date	Project Name	FEI	DUNS	Facility ID	Facility Name
Approve Facility	12/15/2016	NDA-208799-ORIG-1	3003414719	533065822	130002193	TEVA PHARMACEUTICALS INDUSTRIES LIMI
No Further Evaluation	(b) (4)	NDA-208799-ORIG-1	(b) (4)			
Approve Facility	12/12/2016	NDA-208799-ORIG-1	3003414719	533065822	130002193	TEVA PHARMACEUTICALS INDUSTRIES LIMI
Approve Facility	(b) (4)	NDA-208799-ORIG-1	(b) (4)			
No Further Evaluation		NDA-208799-ORIG-1				
Approve Facility		NDA-208799-ORIG-1				
Approve Facility	12/9/2016	NDA-208799-ORIG-1	3005202697	533065806	130001064	TEVA PHARMACEUTICAL INDUSTRIES LIMI
No Further Evaluation	(b) (4)	NDA-208799-ORIG-1	(b) (4)			

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Office of Pharmaceutical Quality

NDA Reviewer Assignment Information

NDA 208799	Established/Proper Name: Fluticasone Proprionate and Salmeterol xinafoate
Dosage Form: *Inhalation Powder*	Strengths: 55/14 mcg/actuation; 113/14mcg/actuation and 232/14 mcg/actuation
Applicant: Teva Pharmaceuticals	Branch IV
BCS Class:	Approximate Goal Date for Primary Review: November 26, 2016
Submission Type: 505b2	Goal Date for Action: March 28 2017
Chemical Type: 5	Cross Referenced Applications: NDAs 205636 and NDA208799

A. PRODUCT/ PROCESS DESCRIPTION (Critical Information for Making Assignments)

This product comprises two APIs in a multidose dry powder inhaler (MDPI). The two APIs are Fluticasone propionate (FP) I, a glucocorticoid already approved as an inhalation powder for oral inhalation for the treatment of asthma and Salmeterol Xinafoate, a long acting beta2-agonist(LABA), also approved for use in other inhalation products. The device in this application is of the device-metered configuration and it is already approved for another Teva drug product (N205636). The application proposes three strengths of the drug and the only excipient is lactose monohydrate.

Office of Pharmaceutical Quality

NDA Reviewer Assignment Information

B. APPLICATION ELEMENTS				
	Initial Assessment	**Yes**	**No**	**Comments**
1.	Accelerated Review expected? (Priority or Breakthrough)		x	
2.	Narrow Therapeutic Index Drug		x	
3.	PET Drug, Drug Device Combination, Liposome product, Biosimiliar product, Novel Dosage Form, Emerging Technology	x		Combination product
4.	Specialty Population (i.e., young children and/or elderly)		x	
5.	Sterile Drug Product (Aseptic, Terminal, Parametric Release)		x	
6.	Use of Models for Release (IVIVC, dissolution models for real time release)		x	
7.	DMF(s) referenced for drug substance?			DMF 15745 for FP DMF (b) (4) Salmeterol
	Never reviewed		x	
	Previously reviewed - acceptable	x		
	Previously reviewed – new amendments	x		

Office of Pharmaceutical Quality

NDA Reviewer Assignment Information

B. APPLICATION ELEMENTS				
	Initial Assessment	Yes	No	Comments
8.	Complex API (Polymeric molecules, Heterogeneous mixtures, Botanical, Antibody-Drug-Conjugate)		x	
9.	Real Time Release Testing, Continuous Manufacturing, PAT		x	
10.	EA Team: • NMEs • API with estrogenic, androgenic, or thyroid activity • API derived from plants or animals • Environmental Assessments		x	

Summarized by *[Electronic Signatures]*

Signature and Date	
Title:	
Print Name:	
Signature and Date:	Julia C. Pinto -S Digitally signed by Julia C. Pinto -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -S, 0.9.2342.19200300.100.1.1=1300366849 Date: 2016.05.17 15:06:09 -04'00'

Office of Pharmaceutical Quality
NDA Reviewer Assignment Information

1 Approvals *[Electronic Signatures]*

Content Reviewers	J. Rondon, L. (OPRO/OE); D. Henry (OPRO/OE);); S. Miller (OPQ/ONDP); O. Stephens (OPQ/ONDP); IQA Steering Committee
Final Approval Signatures and Date	
Division Director, OPRO/OE & LPD, or Designee Title: Branch Chief, OPRO Organizational Excellence (Acting) Print Name: Jorge Rondon Signature and Date: Signature on file	
Authors Title: CMC-Lead/QAL, Branch III, DNDP-I, ONDP Print Name: Stephen Miller Signature and Date: Signature on file Title: Acting Branch Chief, OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII Print Name: Olen Stephens Signature and Date: Signature on file	

2 Document History

Version	**Effective Date**	**Lead Author** *and Working Group*	**Approving Official**	**Summary of Changes**
01	11/11/2015		J. Rondon	Initial