CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208798Orig1s000

OTHER REVIEW(S)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208798 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: ArmonAir RespiClick Established/Proper Name: fluticasone propionate Dosage Form: Inhalation Powder Strengths: 50 mcg, 100 mcg and 200 mcg.		
Applicant: Teva Pharmaceutical Industries Ltd. Agent for Applicant (if applicable): Teva Branded Pharmaceutical Products R&D Inc.		
Date of Application: March 28, 2016 Date of Receipt: March 28, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: January 27, 2017	Action Goal Date (if different):	
Filing Date: May 28, 2016	Date of Filing Meeting: May 16, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Treatment of asthma in patients aged 12 years and older.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into electronic archive.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☐	☒	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible	☒	☐		

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	October 28, 2014
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☒	☐	Studies started in the first quarter of 2016 with results available in the third quarter of 2016
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labeling ☐ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR)	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

format?[4]				
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☒	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☒	☐	☐	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☒ Outer carton label ☒ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted?	☒	☐		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☒	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☒	
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** CDRH-April 5, 2016	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** November 6, 2013 (CMC)	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):**	☐	☒		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐			None

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 28, 2016

BACKGROUND:
Teva is developing fluticasone propionate as an inhalation powder, to be administered through their proprietary multi-dose dry powder inhaler. The product has been developed to have (b) (4) thereby improving lung delivery relative to the currently marketed product Flovent® HFA (GlaxoSmithKline) and DISKUS® (GlaxoSmithKline). The proposed dose strengths are 50, 100, and 200 mcg, twice daily. Fluticasone propionate is indicated for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Musse, Laura	Y
	CPMS/TL:	Barnes, Sandra	N
Cross-Discipline Team Leader (CDTL)	Karimi-Shah, Banu		Y
Division Director/Deputy	Chowdhury, Badrul A.		Y
Office Director/Deputy	Gilbert-McClain, Lydia		Y
Clinical	Reviewer:	Paterniti, Miya	Y
	TL:	Karimi-Shah, Banu	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	He, Lei	Y

	TL:	Marathe, Anshu	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Wang, Yu	Y
	TL:	Levin, Gregory	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jones, Brett	Y
	TL:	Robison, Timothy W.	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Bertha, Craig	Y
	RBPM:	Aisida, Bamidele	N
• Drug Substance	Reviewer:	Stevens, Benjamin	N
• Drug Product	Reviewer:	Shaw, Arthur	N
• Process	Reviewer:	Chiaochun (Joanne) Wang	N
• Microbiology	Reviewer:		
• Facility	Reviewer:	Capacci-Daniel, Christina	N
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Booker, Nyedra	N
	TL:	Williams, Marcia	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Burnett, Taylor	N
	TL:	Klemm, Kathleen	N
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Pringle-Owens, Lissa	N
	TL:	Mistry, Mishale	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable ☐ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☐ Not Applicable ☐ YES ☒ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Lydia Gilbert-McClain, M.D. **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): August 28, 2016 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

LAURA MUSSE
01/19/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208798

Application Type: New NDA

Drug Name(s)/Dosage Form(s): fluticasone propionate, inhalation powder

Applicant: Teva Pharmaceutical Industries Ltd.

Receipt Date: March 28, 2016

Goal Date: January 27, 2017

1. Regulatory History and Applicant's Main Proposals

Teva Pharmaceutical Industries Ltd. is developing fluticasone propionate inhalation powder to be administered through Teva's proprietary multi-dose dry powder inhaler (MDPI) RespiClick inhaler. Their product is intended for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older and will be available in the following three doses, 55, 113 and 232 mcgs. The applicant submitted their proposed draft labeling based on the labels of the RLDs, FLOVENT® DISKUS and ADVAIR® DISKUS, which have been approved for use in the United States. The product proprietary (ArmonAir RespiClick) name was approved on May 11, 2016.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

---

4. Selected Requirements of Prescribing Information

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

N/A 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.
Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.
Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.
Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.
Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.
Comment:

YES 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.
Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.
Comment:

YES 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")
Comment:

Selected Requirements of Prescribing Information

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

YES 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

YES 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

Selected Requirements of Prescribing Information

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

N/A 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 35. All text in the BW should be **bolded**.

Comment:

YES 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

LAURA MUSSE
01/17/2017

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	NDA 208798
Product Name:	ArmonAir RespiClick (fluticasone propionate multi-dose dry powder inhaler (Fp MDPI))
	NDA 208799 AirDuo RespiClick (fluticasone propionate and salmeterol xinafoate multi-dose dry powder inhaler (FS MDPI))
PMR/PMC Description:	Study FSS-PK-10007: Conduct a double-blind (incorporating an open-label comparator), 3-period, crossover study to determine the pharmacokinetic profile and tolerability of single doses of Fp MDPI and FS MDPI compared to Advair Diskus in patients with persistent asthma 4 through 11 years of age.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	Completed
	Trial Completion:	Completed
	Final Report Submission:	12/2019
	Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☒ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

Asthma is a chronic inflammatory disorder of the airways and is a leading chronic disease in children. The safety and efficacy of Fp MDPI and FS MDPI has been established in adults, and those studies support further evaluation of the safety and efficacy in children; this can be done post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The objective is to evaluate the pharmacokinetics of Fp MDPI and FS MPDI in pediatric patients 4-11 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The trial will be a double-blind (incorporating an open-label comparator), 3-period, crossover study to determine the pharmacokinetic profile and tolerability of single doses of Fp MDPI and FS MDPI compared to Advair Diskus in patients with persistent asthma 4 through 11 years of age.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	NDA 208798
Product Name:	ArmonAir RespiClick (fluticasone propionate multi-dose dry powder inhaler (Fp MDPI))
	NDA 208799 AirDuo RespiClick (fluticasone propionate and salmeterol xinafoate multi-dose dry powder inhaler (FS MDPI))
PMR/PMC Description:	Study FSS-AS-30003: Conduct a 12-week, randomized, double-blind, placebo-controlled, efficacy and safety study of Fp MDPI compared with FS MDPI in patients with persistent asthma 4 through 11 years of age.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	Completed
	Trial Completion:	05/2019
	Final Report Submission:	12/2019
	Other:	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☒ Only feasible to conduct post-approval
   ☒ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

Asthma is a chronic inflammatory disorder of the airways and is a leading chronic disease in children. The safety and efficacy of Fp MDPI and FS MDPI has been established in adults, and those studies support further evaluation of the safety and efficacy in children; this can be done post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The objective is to evaluate the efficacy and safety of Fp MDPI and FS MPDI in pediatric patients 4-11 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The trial will be a 12-week, randomized, double-blind, placebo-controlled, efficacy and safety study of Fp MDPI compared with FS MDPI in patients with persistent asthma 4 through 11 years of age.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug

☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

SALLY M SEYMOUR
01/12/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 10, 2017
To:	Badrul Chowdhury, MD, PhD Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Taylor Burnett, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	ARMONAIR RESPICLICK (fluticasone propionate)
Dosage Form and Route:	inhalation powder
Application Type/Number:	NDA 208798
Applicant:	Teva Pharmaceutical Industries Ltd.

1 INTRODUCTION

On March 28, 2016, Teva Pharmaceutical Industries Ltd. submitted for the Agency's review an original New Drug Application (NDA) 208798 for ARMONAIR RESPICLICK (fluticasone propionate) inhalation powder. The proposed indication for ARMONAIR RESPICLICK (fluticasone propionate) inhalation powder is for:

- Maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older.

(b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on December 19, 2016 and May 19, 2016 respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ARMONAIR RESPICLICK (fluticasone propionate) inhalation powder.

2 MATERIAL REVIEWED

- Draft ARMONAIR RESPICLICK (fluticasone propionate) inhalation powder PPI and IFU received on March 28, 2016 and received by DMPP on December 19, 2016.
- Draft ARMONAIR RESPICLICK (fluticasone propionate) inhalation powder PPI and IFU received on March 28, 2016 and received by OPDP on December 19, 2016.
- Draft ARMONAIR RESPICLICK (fluticasone propionate) inhalation powder Prescribing Information (PI) received on March 28, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on December 19, 2016.
- Draft ARMONAIR RESPICLICK (fluticasone propionate) inhalation powder Prescribing Information (PI) received on March 28, 2016, revised by the Review Division throughout the review cycle, and received by OPDP on December 19, 2016.
- Approved FLOVENT HFA (fluticasone propionate) Inhalation Aerosol, for oral inhalation, comparator labeling dated October 5, 2016.
- Approved PROAIR RESPICLICK (albuterol sulfate) inhalation powder, for oral inhalation use, comparator labeling dated September 8, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU document using the Arial font, size 10 and 11 respectively.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
01/10/2017

TAYLOR B BURNETT
01/10/2017

MARCIA B WILLIAMS
01/11/2017

LASHAWN M GRIFFITHS
01/11/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 11, 2017

To: Laura Musse, R.N., M.S., C.R.N.P
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Sadaf Nabavian, Pharm.D.
Regulatory Project Manager
DPARP

From: Taylor Burnett, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Puja Shah, Pharm.D.
Regulatory Review Officer
OPDP

CC: Kathleen Klemm, Pharm.D., RAC
Team Leader
OPDP

Subject: NDA 208798
OPDP labeling comments for ARMONAIR RESPICLICK (fluticasone propionate) inhalation powder FOR ORAL INHALATION USE

In response to DPARP's consult request dated May 19, 2016, OPDP has reviewed the proposed draft labeling (Package Insert [PI] and Carton and Container Labeling) for ARMONAIR RESPICLICK (fluticasone propionate) inhalation powder FOR ORAL INHALATION USE (Armonair) and offers the following comments. OPDP's comments on the proposed Patient Package Insert (PPI) and Instructions for Use (IFU) were provided on January 11, 2017, under separate cover in collaboration with the Division of Medical Policy Programs (DMPP). OPDP's comments on the PI are provided directly below and are based

on the draft marked-up labeling titled "NDA 208798 draft-labeling-final clean.docx" that was provided via email from DPARP on December 19, 2016.

OPDP has also reviewed the proposed carton and container labeling submitted by the sponsor on December 12, 2016, and has the following comments on the proposed the carton, device back label, and draft foil labeling:

- The proposed carton and container labeling includes (b) (4) (b) (4) We note competitor carton and container labeling (e.g., Flovent HFA/Diskus and Arnuity Ellipta) do not contain this presentation. We recommend deletion of this incomplete and misleading risk information from the Airduo carton and container labeling to avoid the implication that this is the full risk disclosure of the drug.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Taylor Burnett at (240) 402-1349 or taylor.burnett@fda.hhs.gov.

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/s/

TAYLOR B BURNETT
01/11/2017

CLINICAL INSPECTION SUMMARY

Date	November 4, 2016
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H. GCPAB Branch Chief
To	Miya Paterniti, M.D., Medical Officer, DPARP Banu Karimi-Shah, Cross-Discipline Team Leader, DPARP Laura Musse, R.N., M.S. C.R.N.P., Regulatory Project Manager, DPARP
NDA	208798, 208799
Applicant	Teva Branded Pharmaceutical Products R&D Inc.
Drug	Fluticasone MDPI, fluticasone MDPI with salmeterol MDPI
NME	No
Therapeutic Classification	Standard
Proposed Indication	Asthma
Consultation Request Date	July 6, 2016 (signed)
Summary Goal Date	October 28, 2016 (revised) Extended: November 4, 2016
Action Goal Date	January 27, 2017
PDUFA Date	January 27, 2017
Carbon Copy:	Central Doc. Rm. DPARP/Division Director/Badrul Chowdhury DPARP /Medical Team Leader/Banu Karimi-Shah DPARP/Medical Officer/Miya Okada Paterniti DPARP/Project Manager/ Laura Musse OSI/Office Director/David Burrow (Acting) OSI/DCCE/ Division Director/Ni Khin OSI/DCCE/Branch Chief/Kassa Ayalew OSI/DCCE/Team Leader/Janice Pohlman/Susan D. Thompson OSI/DCCE/GCP MO/Anthony Orencia OSI/ GCP Program Analyst/Yolanda Patague OSI/Database PM/Dana Walters

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The sponsor for these applications, Teva Branded Pharmaceutical Products R&D, was inspected as requested by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). During

the NDA review, an anonymous source alleged that potential unblinding may have occurred (at the clinical investigator level), due to the presence of a black line on product packaging. The inspection found that the problem was isolated to a single treatment arm (fluticasone-salmeterol 50/12.5 mcg), that impacted only Study Protocol FSS-AS-301 (Study 301). Since no clinical sites were inspected, OSI is not able to assess whether clinical sites were able to, or did differentiate this treatment arm from the other four treatment arms in this study. If sponsor instructions for investigators to remove foil overwrap were followed, there should have been no unblinding of study subjects. The review division is advised to take this report of potential unblinding in one of the five randomized study treatment arms in Study 301 into account, when assessing the results of this study.

The preliminary classification of this sponsor site is No Action Indicated based on communications with the field investigator.

2. BACKGROUND

Teva Branded Pharmaceutical Products R&D, Inc. (Teva), is developing a dry powder inhaler (DPI) formulation of fluticasone propionate (an inhaled corticosteroid) and a combination of fluticasone propionate and salmeterol xinafoate (a long-acting β2 agonist [LABA]), to be administered, using Teva's multi-dose dry powder inhaler (MDPI) device. The safety of the drug product combination is well known and characterized.

The sponsor maintains that Teva's MDPI device is an inhalation-driven device, thereby eliminating the need for coordination of actuation and inspiration in patients with asthma. Additionally, the sponsor suggests that efficacy is comparable with other available analogous marketed products, but doses delivered will be lower.

Two randomized clinical trials were submitted in support of the applicant's NDA. The review division (DPARP) requested inspection of the sponsor site only to review oversight and monitoring of the conducted studies, with specific emphasis placed on blinding methods utilized for investigators and subjects. Coincident with the time of submission of this NDA supplement, after study reports for Study FSS-AS-301 and FSS-AS-30017 had been completed, an allegation of unblinding was communicated by an anonymous source to DPARP. The consult by DPARP did not mention which clinical study site/s were potentially impacted. During the application filing meeting, the review division discussed the allegations and potential for unblinding of treatment assignment to some subjects or clinical investigators by the presence of a black line on the foil overwrap of an (unknown) treatment arm product. No clinical site inspections were requested by the review division.

<u>STUDY FSS-AS-301 (Study 301)</u>
Study FSS-AS-301 was a multicenter, randomized, placebo-controlled efficacy and safety study of multi-dose fluticasone compared with fluticasone/salmeterol multi-dose dry powder inhaler in subjects 12 years and older with persistent asthma.

The primary objective of the study was to evaluate the efficacy of fluticasone propionate (Fp) multi-dose dry powder inhaler (MDPI) and fluticasone salmeterol (FS) MDPI when administered over 12 weeks in patients 12 years of age and older with persistent asthma. Subjects were

randomized to one of the following five treatment arms, administered as one inhalation twice a day: (a) Fp MDPI 50 mcg, (b) Fp MDPI 100 mcg, (c) FS MDPI 50/12.5 mcg, (d) FS MDPI 100/12.5 mcg, and (e) placebo.

The primary efficacy endpoints for this study were: (a) a change from baseline in trough (AM pre-dose and pre-rescue bronchodilator) FEV1, and (b) for the subset of approximately 300 subjects with post-dose serial spirometry, standardized baseline-adjusted area under the effect curve for forced expiratory volume in 1 second from time zero to 12 hours post-dose [FEV1 area under the effect curve (AUEC) from time 0 to 12h], assessed at Week 12 (Treatment Visit 9).

This clinical study was conducted at 129 centers internationally. A total enrollment of 625 subjects was planned (125 subjects for each of the five treatment arms); about 647 subjects were actually enrolled. The study period was from July 23, 2014 to September 21, 2015.

According to the sponsor, treatment for up to 12 weeks with fluticasone propionate MDPI 50 or 100 mcg twice daily or fluticasone-salmeterol MDPI 50/12.5 or 100/12.5 mcg twice daily, was associated with greater improvements in lung function compared with placebo treatment. The data from the serial spirometry subset confirmed the twice-daily dosing regimen as appropriate for both fluticasone propionate MDPI and fluticasone-salmeterol MDPI.

STUDY FSS-AS-30017 (Study 30017)

Study FSS-AS-30017 was a multicenter, randomized, placebo-controlled efficacy and safety study of multi-dose fluticasone compared with fluticasone/salmeterol multi-dose dry powder inhaler in subjects 12 years and older with persistent asthma.

The primary objective of the study was to evaluate the efficacy of fluticasone propionate (Fp) multi-dose dry powder inhaler (MDPI) and fluticasone salmeterol (FS) MDPI when administered over 12 weeks in patients 12 years of age and older with persistent asthma. Subjects were randomized to one of the following treatment arms as one inhalation administered twice daily: (1) Fp MDPI 100 mcg, (2) Fp MDPI 200 mcg, (3) FS MDPI 100/12.5 mcg, (4) FS MDPI 200/12.5 mcg, and (5) placebo MDPI. The primary efficacy measures and endpoints for this study were the same as for Study 301 described above.

This clinical study was conducted at 147 international centers. A total enrollment of 715 subjects was planned; approximately 728 subjects were actually enrolled. The study period was from October 1, 2014 to September 26, 2015.

According to the sponsor, for both study endpoints, improvements were greater in the fluticasone-salmeterol MDPI and fluticasone MDPI groups than in the placebo group, and greater in the fluticasone with salmeterol MDPI groups than in the fluticasone MDPI groups, supporting the additional benefit of the salmeterol in combination with fluticasone. Serial spirometry results showed that the improvements observed in the active treatment groups were sustained over the 12 hours of testing.

3. RESULTS (by site):

Name of sponsor, Address	Protocol #	Inspection Date	Classification
Teva Branded Pharmaceutical Products R&D Inc. Teva Pharmaceutical Industries Ltd. 41 Moores Road Frazer, PA 19355	Protocol FSS-AS-301 647 subjects Protocol FSS-AS-30017 728 subjects	September 28, - October 6, 2016	Pending: Preliminary NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Sponsor

1. **Teva Branded Pharmaceutical Products R&D Inc**.
   Frazer, PA

This inspection was conducted from September 28 to October 6, 2016.

Sponsor records reviewed included the following: transfer of obligation written agreements, clinical study administrative structure involving vendors and clinical supply chains, organizational charts, trial master files, sponsor training slides, standard operating procedures, data management records, clinical supply plans for Study 301 and Study 30017, batch records for fluticasone-salmeterol, pictures of investigational cartons and pouches, and a Quality Assurance (QA) risk assessment report on potential unblinding of investigational product, due to minor differences in cartons used (flat versus glossy finish), and the presence of a black line on the foil pouch overwrap of one dose regimen of investigational product (fluticasone-salmeterol 50/12.5 mcg, 60 doses per inhaler) used in Study 301. Additionally, a root cause analysis of the foil pouch overwrap problem that occurred at the manufacturing facility was reviewed.

Four clinical site records from Study 301 and seven clinical site records from Study 30017 were reviewed for serious adverse events, asthma exacerbation findings, protocol violations, monitoring reports, pre-study visits, and sponsor monitoring oversights.

Also reviewed during inspection were protocol violations and deviations and study site investigational product complaints reported to the sponsor monitor. No observations were reported

to the clinical site sponsor-monitors related to packaging issues such as carton appearance differences, or presence of a black line on foil overwrap of inhalers.

During the course of inspection at the sponsor, evidence was collected, and information obtained by the ORA investigator that the pouch "black line" issue was identified by the Clinical Supply Unit of Teva. A Risk Assessment was conducted by Teva Global Innovative R&D, Quality Assurance Unit (signed off on June 25, 2014, before the commencement of the study). Subsequently, a "root cause" analysis was conducted at the Teva manufacturing facility in Israel and isolated the "black line" mark to a single batch (FS2004, fluticasone-salmeterol 50/12.5 mcg) utilized in Study 301 and corrective actions were implemented for future batches.

Based on a subsequent discussion between sponsor representatives and the FDA investigator on October 4, 2016, (b) (4) units/devices of Batch FS2004 were produced; of these, 940 units/devices were subsequently used for the clinical trial. All 129 subjects randomized to the fluticasone-salmeterol 50/12.5 mcg treatment arm in Study 301 received affected product.

The sponsor's quality assurance unit concluded that there was no concern regarding unblinding of subjects, since the foil pouch was to be removed by the investigator (or site staff) prior to dispensing to subjects. The QA report also concluded that although the black line on the foil patch might isolate (or identify) treatment to one specific treatment arm, the *contents of the affected product* would not be known and clinical investigators would not be unblinded to treatment assignment (in a five arm study). The foil overwrap with the black line affected all subjects in the fluticasone-salmeterol 50/12.5 mcg treatment arm of Study 301 (one of five treatment arms in the study). Photographs obtained from a sponsor representative's e-mail illustrated the black line on an unlabeled pouch and how the black line was subsequently largely obscured (except for perhaps for about a half-inch) by the product label.

OSI communicated with DPARP that although (potential) differentiation of one of five treatment arms in Study 301 may have occurred, the effect (or ability to differentiate treatment) was mitigated somewhat by study design (five treatment arms), and participation of 103 sites with most site enrollments less than 20 subjects. However, since no clinical sites were selected by the review division for inspection, OSI could not confirm that any clinical sites may have identified the difference, and subjects could potentially have been treated differently by the clinical investigator leading to biasing of results. The review division will need to take this risk into account in review of this particular study submitted in support of the application. Additionally, since the clinical investigator or site staff were to remove the foil overwrap, it is unlikely that study subjects were un-blinded.

Review staff from DPARP acknowledged in communications with OSI that they recognize that there is some risk for unblinding, however, it involved only one of the five treatment arms to which subjects were randomized in Study 301 (and not Study 30017). The safety profile of the products involved was well characterized at higher doses than administered during this study. The review division will assess any potential impact of the reported unblinding by examining efficacy of various treatment arms at sites that have subjects randomized to the affected treatment arm.

Based upon the inspection of the sponsor, it appears that only Study 301 was involved with the potential unblinding by investigational product packaging (black line). The problem did not impact Study 30017 since the affected dose was not used in that study. Since no clinical sites were selected for inspection, it is not clear whether site personnel would have been able to, or in fact did differentiate the affected product.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

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/s/

ANTHONY J ORENCIA
11/04/2016

JANICE K POHLMAN
11/04/2016

KASSA AYALEW
11/04/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 25, 2016
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 208798
Product Name and Strength:	ArmonAir RespiClick (Fluticasone Propionate) Dry Powder Inhaler, 55 mcg, 113 mcg, 232 mcg
Product Type:	Drug-Device Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Teva Pharmaceutical Inc.
Submission Date:	March 28, 2016
OSE RCM #:	2016-764
DMEPA Primary Reviewer:	Lissa Owens, PharmD
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review evaluates the proposed container labels, container labeling, prescribing information, and Instructions for Use for ArmonAir RespiClick (Fluticasone Propionate), Dry Powder Inhaler (NDA 208798), submitted on March 28, 2016. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the labels and labeling for areas of vulnerability related to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed labels and labeling to determine whether there are any significant concerns in terms of safety, related to preventable medication errors. We note that the proposed label and labeling can be improved to improve readability and mitigate confusion. Specifically, we note that the proprietary name, ArmonAir, is conditionally acceptable and recommend that the name be included on the labels and labeling. Furthermore, (b) (4), the established name should include the finished dosage form, followed by the strength. Additionally, we note that the strength of the product does not include the corresponding units. Therefore, we provide recommendations in Section 4.2 for the Applicant.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability of important information, promote the safe use of the product, and mitigate any confusion.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Section 2 Dosage and Administration: Highlights and Full Prescribing Information

1. In Table 1, we recommend replacing the abbreviation "BID" with its' intended meaning (twice daily) to prevent misinterpretation and confusion.

B. Section 3 Dosage Forms and Strengths: Highlights and Full Prescribing Information

1. We recommend including the unit of measure (i.e., mcg) after each strength. For example, we recommend revising the statement (b) (4) [redacted] to as follows:

   "Inhalation Powder. FP TRADENAME is a multidose, inhalation-driven, dry powder inhaler for oral inhalation that meters 55 *mcg*, 113 *mcg*, or 232 mcg of fluticasone propionate from the device reservoir and delivers 51 *mcg*, 103 *mcg*, or 210 mcg of fluticasone propionate, respectively, from the mouthpiece per actuation."

4.2 RECOMMENDATIONS FOR TEVA RESPIRATORY, LLC

A. All Labels and Labeling

1. Update the placeholder on the labels and labeling to include the conditionally acceptable proprietary name, 'ArmonAir RespiClick'.
2. As currently presented, the proprietary name appears to include (b) (4) [redacted] Additionally, the established name should include the finished dosage form. Therefore, revise the presentation of the trade name, established name, dosage form, and strength to as follows[1]:

   ArmonAir RespiClick
   (fluticasone propionate inhalation powder)
   55 mcg

   OR

   ArmonAir RespiClick
   (fluticasone propionate) inhalation powder
   55 mcg

[1]See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

OR

ArmonAir RespiClick
(fluticasone propionate)
Inhalation Powder
55 mcg

3. As currently presented, the strength in the colored boxes does not include units. Include the unit of strength in each location where the strength is listed (i.e. 55 mcg vs. 55) to mitigate confusion.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for ArmonAir RespiClick that Teva submitted on March 28, 2016.

Table 2. Relevant Product Information for ArmonAir RespiClick	
Initial Approval Date	N/A
Active Ingredient	Fluticasone Propionate
Indication	• Maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older [redacted] (b) (4)
Route of Administration	Oral Inhalation
Dosage Form	Dry Powder Inhaler
Strength	55 mcg, 113 mcg, and 232 mcg
Dose and Frequency	One inhalation twice a day
How Supplied	A white dry-powder inhaler. Each inhaler has a green cap and is packaged individually in a foil pouch in a carton. Each inhaler contains 0.9g of the formulation and provides 60 actuations.
Storage	Room temperature (between 15º and 25ºC; 59º and 77ºF) in a dry place; excursions permitted from 59ºF to 86ºF (15ºC to 30ºC). Avoid exposure to extreme heat, cold, or humidity.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following ArmonAir RespiClick labels and labeling submitted by Teva on March 28, 2016.

- Prescribing Information (no image)
- Patient Instructions for Use (no image)
- Carton labeling
- Container labels

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[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LISSA C OWENS
07/25/2016

MISHALE P MISTRY
07/25/2016