

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208799Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 208799	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: AirDuo RespiClick Established/Proper Name: Fluticasone Propionate and Salmeterol Xinafoate Dosage Form: Inhalation Powder Strengths: 55/14 mg, 113/14 mg, 232/14 mg		
Applicant: Teva Pharmaceutical Industries Ltd.		
Date of Receipt: March 29, 2016		
PDUFA Goal Date: January 27, 2017		Action Goal Date (if different):
RPM: Sandy Barnes for Laura Musse		
Proposed Indication(s): ^{(b) (4)} treatment of asthma in patients 12 and older.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Advair Diskus	nonclinical pharmacology and toxicology, Human Pharmacokinetics and bioavailability, and General Safety and Efficacy and labeling
Flovent diskus	““”

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

They bridged with a comparative PK study and because it is a DPI and therefore topical they did dose selection study and a long term safety study with Advair Diskus and Flovent Diskus.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO
If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO
If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Advir Diskus	NDA 021077	Y
Flovent diskus	NDA 20833	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a device and new formulation.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If “**NO**”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s): August 23 2016

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph*

IV certification was submitted, proceed to question #15.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

LAURA MUSSE
01/27/2017

**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 12, 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: Karen Dowdy, RN, BSN
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: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): AIRDUO RESPICLICK (fluticasone propionate and salmeterol)

Dosage Form and Route: inhalation powder, for oral inhalation use

Application Type/Number: NDA 208799

Applicant: Teva Branded Pharmaceutical Products R&D Inc. on behalf of Teva Pharmaceutical Industries Ltd.

1 INTRODUCTION

On March 29, 2016, Teva Branded Pharmaceutical Products R&D Inc. on behalf of Teva Pharmaceutical Industries Ltd. submitted for the Agency's review 505(b)(2) New Drug Application (NDA) 208799 for AIRDUO RESPICLICK (fluticasone propionate and salmeterol) inhalation powder. The Reference Listed Drug (RLD) is ADVAIR DISKUS, NDA 021077. The proposed indication for AIRDUO RESPICLICK is for the treatment of asthma in patients aged 12 years and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) on December 19, 2016, and May 27, 2016 respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for AIRDUO RESPICLICK (fluticasone propionate and salmeterol) inhalation powder.

DMPP conferred with the Division of Medication Error Prevention and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on July 26, 2016.

2 MATERIAL REVIEWED

- Draft AIRDUO RESPICLICK (fluticasone propionate and salmeterol) inhalation powder MG and IFU received on March 29, 2016 and received by DMPP and OPDP on December 20, 2016.
- Draft AIRDUO RESPICLICK (fluticasone propionate and salmeterol) inhalation powder Prescribing Information (PI) received on March 29, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 19, 2016.
- Approved ADVAIR DISKUS (fluticasone propionate and salmeterol inhalation powder) comparator labeling dated April 29, 2016.
- Division of Medication Error Prevention and Analysis (DMEPA) Label and Labeling Review for AirDuo RespiClick (fluticasone propionate and salmeterol xinafoate) Dry Powder Inhaler dated July 26, 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.

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 reformatted the MG and IFU documents using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.
- The enclosed IFU review comments are collaborative DMPP and DMEPA.

4 CONCLUSIONS

The MG 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 MG 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 MG and IFU.

Please let us know if you have any questions.

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

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/s/

KAREN M DOWDY
01/12/2017

TAYLOR B BURNETT
01/12/2017

MARCIA B WILLIAMS
01/13/2017

LASHAWN M GRIFFITHS
01/13/2017

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
-

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)

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?

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- 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
-

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)

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/s/

SALLY M SEYMOUR
01/12/2017

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 # 208799 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: AirDuo RespiClick (proposed) Established/Proper Name: Fluticasone Propionate and Salmeterol Xinafoate Dosage Form: Inhalation Powder Strengths: 55/14 mcg, 113/14 mcg and 232/14 mcg.		
Applicant: Teva Pharmaceutical Industries Ltd. Agent for Applicant (if applicable): Teva Branded Pharmaceutical Products R&D Inc.		
Date of Application: March 29, 2016 Date of Receipt: March 29, 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 <u>not</u> 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:		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	☐ 351(a) ☐ 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	☐ Standard ☐ Priority
The application will be a priority review if:	☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
• 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	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐	☐ 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)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ 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				

<i>to the supporting IND(s) if not already entered into electronic archive.</i>				
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)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	☒	☐	☐	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> 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?	☒	☐		
<u>User Fee Status</u> <i>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.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>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.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	☒	☐		

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)]?		☐	☒		
<i>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.</i>					
• 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		
<i>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.</i>					
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)]?	☐	☐	☒		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☐	☐	☒		
If yes , # years requested:					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
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)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>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.</i>	☐	☐	☒	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ 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				
<i>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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
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)?	☒	☐		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☒	☐		
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>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].</i> <i>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...”</i>	☒	☐	☐	
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? <i>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)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	
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)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>	☒	☐		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

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<i>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.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☒	☐	☐	October 28, 2014
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☒	☐	Studies started in the first quarter of 2016 with results available in the third quarter of 2016
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>	☐	☒		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☒	☐	☐	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	☐	☒	☐	
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? <i>If no, request applicant to submit SPL before the filing date.</i>	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR)	☒	☐		

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<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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☒	☐	☐	
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? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	☒	☐	☐	
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? (<i>send WORD version if available</i>)	☒	☐	☐	
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?	☒	☐		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☒	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☒	
<i>If no, request in 74-day letter.</i>				
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)	☒	☐	☐	
<i>If yes, specify consult(s) and date(s) sent:</i> 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 a fluticasone propionate/salmeterol combination product, using its proprietary multi-dose dry powder inhaler. This product has been developed to (b) (4) thereby improving lung delivery relative to the currently marketed product ADVAIR® DISKUS® (fluticasone/salmeterol, GlaxoSmithKline).

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:	Pinto, Julia	Y
	RBPM:	Aisida, Bamidele	N
• Drug Substance	Reviewer:	Stevens, Benjamin	N
• Drug Product	Reviewer:	Shen, Xiaobin	Y
• Process	Reviewer:	Rogers, Brian	N
• Microbiology	Reviewer:	Sun, Zhigang	N
• 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:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Lissa Pringle-Owens	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: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ 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: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>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</i>	☐ 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 (NDAs only)</u> 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 (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> 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. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ 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 ADRAAs completed: April 2016

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/s/

LAURA MUSSE
01/12/2017

**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

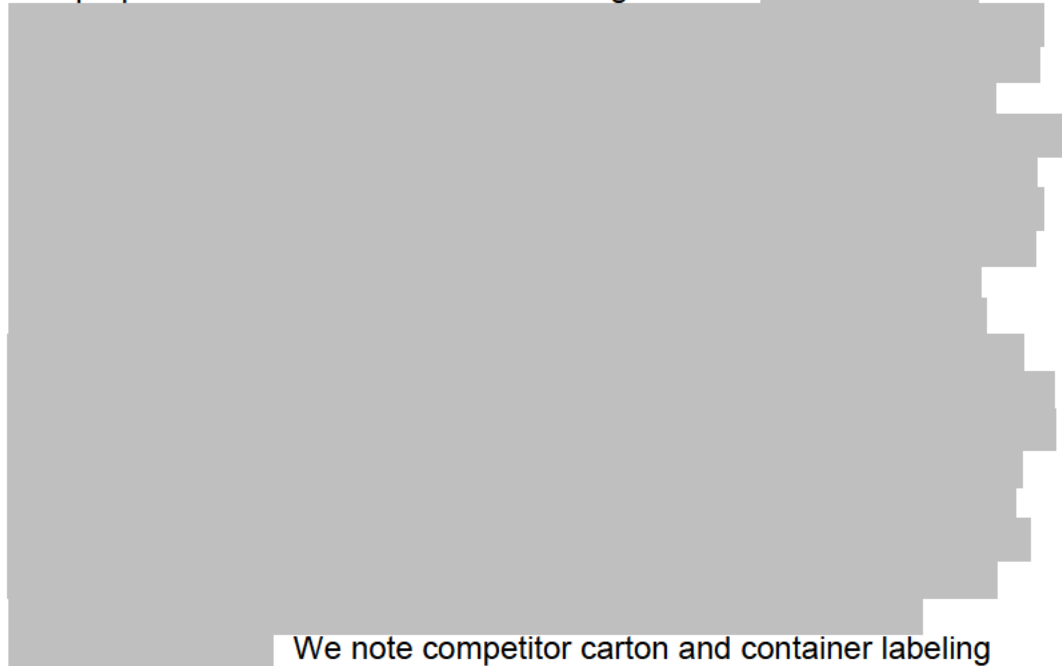
Subject: NDA 208799
OPDP labeling comments for AIRDUO RESPICLICK (fluticasone propionate and salmeterol) inhalation powder FOR ORAL INHALATION USE

In response to DPARP's consult request dated May 27, 2016, OPDP has reviewed the proposed draft labeling (Package Insert [PI] and Carton and Container Labeling) for AIRDUO RESPICLICK (fluticasone propionate and salmeterol) inhalation powder FOR ORAL INHALATION USE (Airduo) and offers the following comments. OPDP's comments on the proposed Patient Package Insert (PPI) and Instructions for Use (IFU) will be provided at a later date 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 208799 draft-prescribing-info - 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 March 29, 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)



We note competitor carton and container labeling (e.g., Advair Diskus and Breo 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.

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

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/s/

TAYLOR B BURNETT
01/11/2017

CLINICAL INSPECTION SUMMARY

Date	November 4, 2016
From	Anthony Orenca 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 Orenca 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 β_2 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.

STUDY FSS-AS-301 (Study 301)

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 Orenca, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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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 26, 2016

Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Application Type and Number: NDA 208799

Product Name and Strength: AirDuo RespiClick (fluticasone propionate and salmeterol xinafoate) Dry Powder Inhaler
55 mcg/14 mcg, 113 mcg/14 mcg, 232 mcg/14 mcg

Product Type: Drug-Device Combination Product

Rx or OTC: Rx

Applicant/Sponsor Name: Teva Pharmaceutical Inc.

Submission Date: March 29, 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 AirDuo RespiClick (fluticasone propionate and salmeterol xinafoate), Dry Powder Inhaler (NDA 208799), submitted on March 29, 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.

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 increase readability and mitigate confusion. Specifically, we note that the proprietary name, AirDuo, 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. We also note that the Applicant is proposing to utilize the same color block for the corresponding strengths as their proposed product, ArmonAir RespiClick. Given that the proposed product ArmonAir RespiClick contains one of the active ingredients contained in AirDuo RespiClick, we recommend further distinguishing these products to mitigate the potential for wrong drug errors. Additionally, we note that the strength of the product does not include the corresponding units on the labels and labeling. Therefore, we provide recommendations in Section 4.1 for the Division and 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 [REDACTED] (b) (4)

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] to as follows:

“Inhalation Powder. FS TRADENAME is a multidose, inhalation-driven, dry powder inhaler for oral inhalation that meters 55 *mcg*, 113 *mcg*, or 232 *mcg* of fluticasone propionate and 14 *mcg* of salmeterol from the device reservoir and delivers 49 *mcg*, 100 *mcg*, or 202 *mcg* of fluticasone propionate and 12.75 *mcg* of salmeterol 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, ‘AirDuo RespiClick’.
2. As currently presented, the proprietary name appears to include [REDACTED] (b) (4). 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 follows¹:

AirDuo RespiClick
(fluticasone propionate and salmeterol xinafoate inhalation powder)
55 mcg/14 mcg

¹See 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>

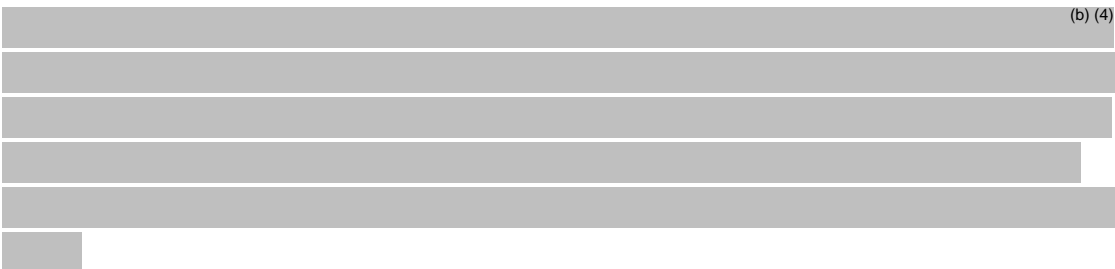
OR

AirDuo RespiClick
(fluticasone propionate and salmeterol xinafoate) inhalation powder
55 mcg/14 mcg

OR

AirDuo RespiClick
(fluticasone propionate and salmeterol xinafoate)
Inhalation Powder
55 mcg/14 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/14 mcg vs. 55/14) to mitigate confusion.

4.  (b) (4)

5. To increase readability, we recommend that the strength is presented in one color and the font size is increased to match the font size of the fluticasone strength. Currently,  (b) (4), and may be overlooked.

B. Section 16.1 How Supplied: Full Prescribing Information

1. You state in this section “FS TRADENAME is supplied in the following three strengths as a white dry-powder inhaler. Each inhaler has a  cap and is packaged individually in a foil pouch in a carton. Each inhaler contains 0.45 g of the formulation and provides 60 actuations.” However, per your Quick Reference Guide and Instructions for Use labeling, the inhaler cap is yellow for this proposed product. Please clarify if the cap is  or yellow and revise accordingly to ensure consistency.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for AirDuo RespiClick that Teva submitted on March 29, 2016.

Table 2. Relevant Product Information for AirDuo RespiClick	
Initial Approval Date	N/A
Active Ingredient	Fluticasone Propionate and Salmeterol Xinafoate
Indication	(b) (4) treatment of asthma in patients 12 years of age and older
Route of Administration	Oral Inhalation
Dosage Form	Dry Powder Inhaler
Strength	55 mcg/14 mcg, 113 mcg/14 mcg, 232 mcg/14 mcg
Dose and Frequency	One inhalation twice a day
How Supplied	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
Storage	Room temperature (between 15° and 25°C; 59° and 77°F) in a dry place; excursions permitted from 59°F to 86°F (15°C to 30°C). Avoid exposure to extreme heat, cold, or humidity.

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 AirDuo RespiClick labels and labeling submitted by Teva on March 29, 2016.

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

(b) (4)



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

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LISSA C OWENS
07/26/2016

MISHALE P MISTRY
07/26/2016