

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205636Orig1s000**

**OTHER REVIEW(S)**

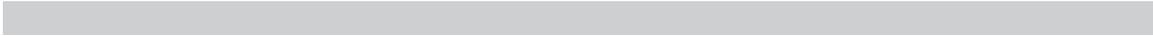
**505(b)(2) ASSESSMENT**

| <b>Application Information</b>   |                      |                                  |
|--|----------------------|----------------------------------|
| NDA # 205636   | NDA Supplement #: S- | Efficacy Supplement Type SE-     |
| Proprietary Name: ProAir RespiClick<br>Established/Proper Name: albuterol sulfate<br>Dosage Form: powder for inhalation<br>Strengths: 90 mcg   |                      |                                  |
| Applicant: Teva Branded Pharmaceuticals  |                      |                                  |
| Date of Receipt: March 06, 2015  |                      |                                  |
| PDUFA Goal Date: May 06, 2015  |                      | Action Goal Date (if different): |
| RPM: Leila P. Hann   |                      |                                  |
| Proposed Indication(s): 1. Treatment or prevention of bronchospasms in patients 12yrs and older with reversible obstructive pulmonary disease<br>2. Prevention of exercised-induced bronchospasm in patients 12yrs 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)           |
|---|--|
| ProAir HFA, NDA021457   | FDA's previous finding of safety and effectiveness (e.g., clinical or nonclinical or both) |

\*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 literature<sup>1</sup>. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

Crossover study with ProAir HFA

**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).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

<sup>1</sup>For 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) |
|---------------------|------------|--|
| ProAir HFA          | NDA 021457 | Y  |
| Proventil-HFA       | NDA 020503 | 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).*

Name of drug(s) approved in a 505(b)(2) application: ProAir HFA

- 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 new dosage form, from metered dose inhalation aerosol to multi-dose dry powder inhaler

*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): Proventil-HFA (NDA020503), Ventolin HFA (NDA020983), Accuneb (NDA020949) , and approved generics are listed in the Orange Book.

**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): Proventil-HFA/5775321,  
Proventil-HFA/6006745, and Proventil-HFA 5605674

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): 5605674

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):

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): 5775321 and 6006745
- (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): 01/19/2015

*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

Drafted: L. Hann/ January 05, 2015; March 11, 2015  
Cleared: S. Barnes/ January 06, 2015; March 10, 2015  
505b2 Committee: March 18, 2015  
Finalized: L. Hann/ March 30, 2015

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/s/  
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LEILA P HANN  
03/30/2015

## 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 # 205636  
Product Name: ProAir RespiClick (Albuterol MDPI)

---

PMR/PMC Description: Conduct a study to assess the efficacy and safety of chronic dosing of ProAir RespiClick in pediatric asthma patients 4 to 11 years

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Study ABS-AS-303:

PMR/PMC Schedule Milestones: Final Report Submission: 09/30/2015

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

The PMR is for a PREA study in pediatric patients. Review of adult and adolescent data has established efficacy and safety and supports conducting trials in younger pediatric patients.

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 goal of the study is to evaluate the safety and efficacy of chronic dosing of ProAir RespiClick in children 4 to 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.

Study ABS-AS-303 is a Phase 3, double-blind, placebo-controlled, parallel-group, repeat-dose study evaluating chronic-dose efficacy and safety (3 weeks duration)

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.*

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/s/  
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SALLY M SEYMOUR  
03/27/2015

## 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 # 205636  
Product Name: ProAir RespiClick (Albuterol MDPI)

---

PMR/PMC Description: Conduct a study to assess the efficacy and safety of two dose levels of ProAir RespiClick in pediatric asthma patients 4 to 11 years of age.

---

Study ABS-AS-202:

PMR/PMC Schedule Milestones: Final Report Submission: 09/30/2015

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

The PMR is for a PREA study in pediatric patients. Review of adult and adolescent data has established efficacy and safety and supports conducting trials in younger pediatric patients.

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 goal of the study is to evaluate the safety and efficacy of two doses of ProAir RespiClick in children 4 to 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.

Study ABS-AS-202 is a double-blind, placebo-controlled, single-dose, 5-treatment, 5-way crossover efficacy and safety study comparing 2 dose levels of ProAir Respiclick.

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
- 

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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
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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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SALLY M SEYMOUR  
03/27/2015

## PMR/PMC Development Template

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NDA # 205636  
Product Name: ProAir RespiClick (Albuterol MDPI)

---

PMR/PMC Description: Conduct a study to assess the pharmacokinetics of ProAir RespiClick in pediatric asthma patients between the ages 4 to 11 years

---

Study ABS-AS-102:  
PMR Schedule Milestones: Final Report Submission: 09/30/2015

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

The PMR is for a PREA study in pediatric patients. Review of adult and adolescent data has established efficacy and safety and supports conducting trials in younger pediatric patients.

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 goal of the study is to evaluate the pharmacokinetics of ProAir compared to ProAir HFA in children 4 to 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.

Study ABS-AS-102 is a Phase 1 open-label, single-dose, 2-way crossover comparative pharmacokinetic (PK) study of Albuterol MDPI and ProAir HFA

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  
Comparative pharmacokinetic (PK) study
- 

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.*

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/s/  
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SALLY M SEYMOUR  
03/27/2015

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

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

**Memorandum**

**Date:** February 25, 2015

**To:** Leila Hann  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
(DPARP)

**From:** Matthew Falter, Pharm.D.  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Kathleen Klemm, Pharm.D., RAC  
Group Leader, OPDP

**Subject:** OPDP Labeling Consult Response  
NDA # 205636  
PROAIR RESPICLICK (albuterol sulfate) inhalation powder

---

In response to DPARP's, June 3, 2014, consult request, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and Carton/Container labeling for PROAIR RESPICLICK (albuterol sulfate) inhalation powder (Proair Respiclick).

OPDP has reviewed the proposed PI. Our comments on the proposed PI are based on the proposed draft-marked up labeling titled "2015\_02\_11NDA205636Label.doc", which was sent via e-mail from DPARP to OPDP on February 12, 2015. OPDP comments on the proposed PI are provided directly in the marked-up document attached (see below).

OPDP has reviewed the proposed Carton and Container Labeling submitted by the applicant and available in the EDR at:

- <\\cdsesub1\evsprod\nda205636\0013\m1\us\draft-cart-trade-opening.pdf>
- <\\cdsesub1\evsprod\nda205636\0013\m1\us\draft-cont-trade.pdf>
- <\\cdsesub1\evsprod\nda205636\0013\m1\us\draft-foil-trade.pdf>
- <\\cdsesub1\evsprod\nda205636\0013\m1\us\draft-cart-sample-opening.pdf>
- <\\cdsesub1\evsprod\nda205636\0013\m1\us\draft-cont-sample.pdf>
- <\\cdsesub1\evsprod\nda205636\0013\m1\us\draft-foil-sample.pdf>

OPDP offers the following comment on the proposed Carton labels.

- We note the proposed carton labels contain the phrase (bolded emphasis original), **“IMPORTANT INFORMATION”** followed by a summary of some of the Warnings and Precautions from the proposed PI regarding the worsening of symptoms. We are concerned from a promotional perspective that the phrase “Important Information” does not adequately convey that the information that follows is risk information, thereby minimizing these risks.
- The misleading nature of this presentation is further confounded by the term (bolded emphasis original), **“IMPORTANT”** followed by information regarding when the inhaler should be discarded. We note that this information is presented in bolded red font and on the same panel of the proposed carton labels as the risk information. In contrast, the risk information is only presented in regular font, without emphasis.
- Therefore, OPDP recommends the following:
  - Revising the phrase **“IMPORTANT INFORMATION”** to read **“IMPORTANT RISK INFORMATION”** or **“IMPORTANT SAFETY INFORMATION”**
  - Removing emphasis from the information regarding when the inhaler should be discarded.

OPDP has no comments on the proposed Container labels at this time.

OPDP’s review and comments on the proposed PPI and proposed IFU was conducted jointly with the Division of Medical Policy Programs (DMPP). This review was provided under separate cover and submitted into DARRTS on February 24, 2015.

Thank you for the opportunity to comment on the proposed labeling. If you have any questions regarding this review, please contact me at [matthew.falter@fda.hhs.gov](mailto:matthew.falter@fda.hhs.gov) or at 6-2287.

13 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/  
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MATTHEW J FALTER  
02/25/2015

**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: February 24, 2015

To: **Badrul Chowdhury, M.D., Director  
Division of Pulmonary, Allergy and Rheumatology  
(DPARP)**

Through: **LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
Division of Medical Policy Programs (DMPP)**

**Melissa Hulett, MSBA, MSN, FNP-BC, RN  
Team Leader, Patient Labeling  
Division of Medical Policy Programs (DMPP)**

From: **Twanda Scales, RN, BSN, MSN/Ed.  
Patient Labeling Reviewer  
Division of Medical Policy Programs (DMPP)**

**Kathleen Klemm, Pharm.D., RAC  
Team Leader  
Office of Prescription Drug Promotion (OPDP)**

Subject: **DMPP Review of Patient Labeling: Patient Package Insert  
(PPI) and Instructions for Use (IFU)**

Drug Name (established name): **PROAIR RESPICLICK (albuterol sulfate)**

Dosage Form and Route: **Inhalation Powder**

Application Type/Number: **NDA 205636**

Applicant: **Teva Pharmaceuticals (Teva)**

## 1 INTRODUCTION

On May 5, 2014, Teva submitted, for the Agency's review, a New Drug Application for NDA 205636, PROAIR RESPICLICK (albuterol sulfate) Inhalation Powder. PROAIR RESPICLICK (albuterol sulfate) Inhalation Powder is indicated for treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 12 years of age 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 request by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) on May 27, 2014, and June 3, 2014, respectively for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for PROAIR RESPICLICK (albuterol sulfate) Inhalation Powder.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and DMEPA deferred to DMPP to provide IFU review comments.

## 2 MATERIAL REVIEWED

- Draft PROAIR RESPICLICK (albuterol sulfate) Inhalation Powder PPI and IFU received on May 5, 2014, and received by DMPP on February 12, 2015.
- Draft PROAIR RESPICLICK (albuterol sulfate) Inhalation Powder PPI and IFU received on May 5, 2014, and received by OPDP on February 12, 2015.
- Draft PROAIR RESPICLICK (albuterol sulfate) Inhalation Powder Prescribing Information (PI) received on May 5, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on February 12, 2015.
- Draft PROAIR RESPICLICK (albuterol sulfate) Inhalation Powder Prescribing Information (PI) received on May 5, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on February 12, 2015.
- Approved PROAIR HFA (albuterol sulfate) Inhalation Aerosol comparator labeling approved March 7, 2012.
- DMEPA PROAIR RESPICLICK Albuterol Human Factors Validation Study Review dated January 16, 2015.

## 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 APFont to make medical information more

accessible for patients with vision loss. We have reformatted the PPI and IFU documents using the Arial font, size 11.

In our 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 are consistent with the approved comparator labeling where applicable
- 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 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/  
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SHARON W WILLIAMS  
02/24/2015

KATHLEEN KLEMM  
02/24/2015

MELISSA I HULETT  
02/24/2015

LASHAWN M GRIFFITHS  
02/24/2015

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**HUMAN FACTORS VALIDATION STUDY 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\*\*\***

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**Date of This Review:** January 16, 2015

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

**Application Type and Number:** NDA 205636

**Product Name and Strength:** ProAir RespiClick (Albuterol Sulfate) Inhalation Powder  
90 mcg per actuation

**Product Type:** Single-Ingredient Product

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Teva Respiratory, LLC.

**Submission Date:** May 5, 2014

**OSE RCM #:** 2014-2393

**DMEPA Reviewer** Sherly Abraham, R.Ph.

**DMEPA Team Leader:** Kendra Worthy, Pharm.D.

**Human Factors Specialist:** QuynhNhu Nguyen, MS

**DMEPA Associate Director:** Lubna Merchant, M.S., Pharm.D.

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## 1 REASON FOR REVIEW

This review is in response to a request by DPARP to review human factors study results report and Phase 3 clinical trial complaint report that is submitted with this NDA. The applicant is proposing to market a new Multidose Dry Powder Inhaler (MDPI) Proair Respiclick to deliver a controlled dose of short-acting beta agonist albuterol to the pulmonary system in order to relieve a bronchospasm.

## 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.

| <b>Table 1. Materials Considered for this Label and Labeling Review</b> |   |
|---|---|
| <b>Material Reviewed</b>  | <b>Appendix Section (for Methods and Results)</b> |
| Product Information/Prescribing Information                             | A   |
| FDA Adverse Event Reporting System (FAERS)                              | B-N/A   |
| Previous DMEPA Reviews  | C   |
| Human Factors Study   | D   |
| ISMP Newsletters  | E-N/A   |
| Phase 3 clinical trial complaint report                                 | F   |
| Labels and Labeling   | G   |

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant is proposing to market a new Multidose Dry Powder Inhaler (MDPI) Proair Respiclick to deliver a controlled dose of short-acting beta agonist albuterol to the pulmonary system in order to relieve a bronchospasm. The product provides an alternative for those patients who cannot use pressurized metered dose inhalers (pMDI) correctly due to the challenges of effectively coordinating inspiration and actuation.

The applicant followed an iterative process during the design of the MDPI in which they revised the Instructions for Use (IFU) to address the user errors observed during the formative human factor study. The results of the human factors validation/summative study showed some use errors associated with the inhalation technique, not opening the cover fully, and not closing the

cover in between inhalations. However, the study results also showed that the use performance was improved in subsequent inhalation attempts when they checked the IFU, which indicated that the users were able to correct the errors associated with the inhalation technique.

The more concerning use errors were not opening the cover fully (1 use error) and not closing the cover between inhalations (15 use errors). When the cover is not opened fully i.e. a clicking should be heard by the user, the device does not dispense a metered dose from the drug reservoir and is not ready for inhalation. When the cover is not closed in between inhalations, the device would not dispense the successive doses of medication, and the number of doses shown on the dose counter may remain unchanged without the user's notice. These use errors, if not aware by the user, can lead to repeated underdosing, which is considered as catastrophic. We recommend that the Sponsor provide additional emphasis on the information within the IFU regarding the importance of performing those two steps properly as described in section 4.1.

Additionally, we reviewed the Phase 3 clinical trial complaint report submitted by the Sponsor. There were 5652 devices in total used across the five clinical studies and 27 were complaint samples and seven were due diligence samples. Most of the complaints were related to the patient misuse of the device (See Table 3 in Appendix F). However, Nine (9) clinical samples reported that the patient did not feel delivery of medication. These devices were thoroughly investigated and the root causes were identified; Five (5) devices were attributed to patient dose perception, where the dose was delivered but the patients did not "feel" that a dose was delivered. Four (4) devices were attributed to patient operational fault; two patients did not inhale the dose as instructed, one patient most likely did not close the mouthpiece cover before taking a second dose and one patient most likely exhaled into the device before dose inhalation.

These similar task failures were also observed in the validation study. These concerns are already addressed in IFU and we are providing additional comments in section 4.1 to emphasize the closing of the mouthpiece after each inhalation and to verify the dose counter to ensure a dose is administered. Out of the eight cases of dose counter issues, one was from clinical complaint and seven were due diligence reports from Teva. We note that all of the devices were functioning as intended; however, not closing the cap in between inhalations may have been the root cause of these dose counters issues. Therefore, we are providing additional recommendation to verify the dose counter in step 5 of the IFU.

#### **4 CONCLUSION & RECOMMENDATIONS**

DMEPA concludes that the Human Factors Summative Validation Study Results are generally acceptable with the exception of use errors associated with opening the cap and closing the cap in between inhalations. We recommend that the Sponsor provide additional emphasis on the information within the IFU regarding the importance of performing those two steps properly as described in section 4.1. DMEPA recommends the following comments to be implemented to the IFU prior to approval.

##### **4.1 RECOMMENDATIONS FOR TEVA RESPIRATORY, LLC.**

Add the following information within specified sections of Instruction for Use to emphasize information regarding the opening and closing of the cap:

###### **A. Introduction section:**

Add the following sentences below the [REDACTED] (b) (4)

1. "A click sound should be heard when the cap is opened fully and if not, the inhaler may not be activated to dispense a metered dose."

###### **B. Important information on [REDACTED] (b) (4)**

2. Revise the first statement to include "Always close the cap after each inhalation so your inhaler will be ready for you to take your next dose. Do not open the cap unless you are....."

###### **C. Step-by-step instructions section:**

Add the following sentence to step 5 after the last sentence to hold the breath for 10 seconds:

3. "Check the dose counter on the back of the inhaler to make sure you received the dose."

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for ProAir RespiClick that Teva Respiratory LLC submitted on May 5, 2014.

| <b>Table 2. Relevant Product Information for ProAir RespiClick</b> |   |
|--|---|
| <b>Initial Approval Date</b>                                       | N/A   |
| <b>Active Ingredient</b>   | Albuterol Sulfate   |
| <b>Indication</b>  | Treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease. Prevention of exercise-induced bronchospasm in patients 12 years of age and older |
| <b>Route of Administration</b>                                     | Oral Inhalation   |
| <b>Dosage Form</b>   | Inhalation Powder   |
| <b>Strength</b>  | 90 mcg per actuation  |
| <b>Dose and Frequency</b>  | One to two inhalations every 4 to 6 hours or<br>Two inhalations 15 to 30 minutes before exercise  |
| <b>How Supplied</b>  | Dry powder inhaler in boxes of one  |
| <b>Storage</b>   | Room temperature (between 15° and 25°C; 59° and 77°F)   |

## **APPENDIX C. PREVIOUS DMEPA REVIEWS**

### **C.1 Methods**

We searched the L drive on January 14, 2015, using the terms, ProAir RespiClick to identify reviews previously performed by DMEPA.

### **C.2 Results**

Our search identified one previous review<sup>1</sup>, in which we provided recommendations for the labels; these recommendations have not been implemented at the time of this review.

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<sup>1</sup>Owens, L. Label and Labeling Review for ProAir RespiClick (NDA 205636). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 12 10. 32 p. OSE RCM No.: 2014-1181.

## **APPENDIX D. HUMAN FACTORS STUDY**

### **D.1 Study Design**

Development of the MDPI included an analytical review, risk assessment and formative empirical assessment. The formative study was conducted to assess whether representative users could use the inhaler safely and effectively by referring to the IFU and included simulated-use testing and individual in-depth interviews.

Validation studies were carried out with 70 participants representative of potential users in four study centers across the US.

The participant demographics included:

52 Adults, 18 Pediatric patients with caregivers

36 Males, 34 Females

Ages ranged from 7 years -72 years

36 Asthma patients, 16 COPD patients, and 18 Inhaler naïve healthy volunteers

All participants were provided with an unused MDPI inhaler individually sealed in a foil pouch, inside a cardboard carton with the IFU and were instructed to take as long as they needed to look in the pack and read instructions as if they were going to use the inhaler for the first time. A worse case realistic training approach was applied to all participant groups, where the only form of training was through the use of the IFU. For pediatric patients, their accompanying parent or guardian was told to provide the same level of assistance as they would normally provide at home. Participants were interviewed by an experienced human factor moderator and observed via a one-way mirror.

### **D.2 Results**

All 70 participants included in the validation study used the MDPI inhaler two or more times during the study session. The study results showed that 65/70 participants were successful during the first task attempt, 68/70 participants were successful during the second task attempt due to increased familiarity and improved competence. All participants demonstrated successful use of the MDPI inhaler during the study session. 5/70 of the participants who failed the first time had safety critical errors:

- Incomplete opening of the mouthpiece cover on first attempt
- Obstruction of the inlet vent with top lip on second attempt
- Slight inversion of device when opening the mouthpiece cover on first attempt
- Did not position mouthpiece in mouth for inhalation on first attempt
- Clear inversion of device when opening the mouthpiece cover on first attempt
- Appeared to exhale into mouthpiece and did not inhale on second attempt
- Exhaled into mouthpiece and did not inhale on first attempt.

## APPENDIX F. Phase 3 Clinical Complaint Report

### F.1 Methods

We reviewed the Phase 3 clinical trial complaint report submitted by the Sponsor.

### F.2 Results

There were 5652 devices in total used across the five clinical studies and 27 were complaint samples and seven were due diligence samples. All reported complaint cases are summarized below in Table 3:

**Table 3: Summary of All Reported Cases from Phase 3 Complaint Report (n=34)**

| Complaint                     | Root Cause  |
|-------------------------------|---|
| Mouthpiece cover issues (n=8) | Misuse/handling by patient (n=5), damage due to high impact force (n=2), patient had difficulty closing the cover (n=1)   |
| Dose delivery issues (n=9)    | Issues with patient dose delivery perception (n=5), patient inhalation issues (n=2), patient exhaling and cause powder buildup (n=1), patient not closing the mouth piece cover before taking the second dose (n=1) |
| Patient discomfort (n=4)      | Plastic component touching lip when inhaling a dose (n=4)   |
| Dose counter issues (n=8)     | Patient diary discrepancies found by Teva (n=7), reported by patient and no root cause given (n=1). Investigation found all devices functioned as intended.   |
| Water damage (n=5)            | Patient misuse/handling (n=5)   |

## **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,<sup>2</sup> along with post market medication error data, we reviewed the following ProAir RespiClick labels and labeling submitted by Teva Respiratory LLC submitted on May 5, 2014.

- Instructions for Use

### **G.2 Label and Labeling Images**

(b) (4)



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

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SHERLY ABRAHAM  
01/16/2015

LUBNA A MERCHANT  
01/16/2015

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## **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\*\*\***

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**Date of This Review:** December 10, 2014

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

**Application Type and Number:** NDA 205636

**Product Name and Strength:** ProAir RespiClick (Albuterol Sulfate) Inhalation Powder  
90 mcg per actuation

**Product Type:** Single-Ingredient Product

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Teva Respiratory, LLC.

**Submission Date:** May 5, 2014

**OSE RCM #:** 2014-1181

**DMEPA Primary Reviewer:** Lissa C. Owens, PharmD

**DMEPA Team Leader:** Kendra Worthy, PharmD

---

## 1 REASON FOR REVIEW

This review evaluates the proposed container labels, carton labeling, prescribing information, and instructions for use for ProAir RespiClick (Albuterol Sulfate) Inhalation Powder for risk of medication error in response to a request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). DPARP requested this as part of their evaluation for new NDA 205636.

## 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.

| <b>Table 1. Materials Considered for this Label and Labeling Review</b> |   |
|---|---|
| <b>Material Reviewed</b>  | <b>Appendix Section (for Methods and Results)</b> |
| Product Information/Prescribing Information                             | A   |
| FDA Adverse Event Reporting System (FAERS)                              | B   |
| Previous DMEPA Reviews  | N/A   |
| Human Factors Study   | N/A   |
| ISMP Newsletters  | N/A   |
| Other   | N/A   |
| Labels and Labeling   | G   |

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

ProAir is currently marketed (ProAir HFA) utilizing a different device. The RespiClick device is not currently marketed with any other product. We did not retrieve any errors related to label and labeling with the currently marketed ProAir.

We performed a risk assessment of the proposed container labels, carton and insert labeling, and instructions for use to identify deficiencies that may lead to medication errors.

DMEPA finds the proposed container labels, insert labeling, and instructions for use acceptable. However, the strength located on the carton labeling could be improved.

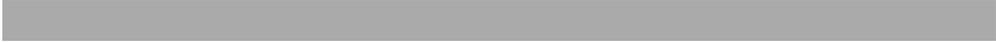
## 4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container labels, insert labeling, and instructions for use are acceptable. However, the proposed carton labeling can be improved to increase the

prominence of important information on the label to promote the safe use of the product. We provide the following recommendations in Section 4.1

#### **4.1 RECOMMENDATIONS FOR TEVA**

##### **A. All Label and Labeling**

1. Utilize the same font color of the name 'ProAir' in the name 'RespiClick'. As presented  (b) (4)  
  


##### **B. Carton Labeling**

1. Relocate the strength from the bottom of the labeling to after the dosage form so that it is easily recognized: see example below

ProAir RespiClick  
(Albuterol Sulfate) Inhalation Powder  
90 mcg

2. Relocate the statement 'With Dose Counter' to below the graphic to allow for the placement of the strength statement.
3. Consider utilizing a different color (other than red) to avoid potential confusion between this product and the currently marketed ProAir HFA which also utilizes a red color.

#### 4. APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

##### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for ProAir RespiClick that Teva Respiratory LLC submitted on May 5, 2014.

| <b>Table 2. Relevant Product Information for ProAir RespiClick</b> |   |
|--|---|
| <b>Initial Approval Date</b>                                       | N/A   |
| <b>Active Ingredient</b>   | Albuterol Sulfate   |
| <b>Indication</b>  | Treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease. Prevention of exercise-induced bronchospasm in patients 12 years of age and older |
| <b>Route of Administration</b>                                     | Oral Inhalation   |
| <b>Dosage Form</b>   | Inhalation Powder   |
| <b>Strength</b>  | 90 mcg per actuation  |
| <b>Dose and Frequency</b>  | One to two inhalations every 4 to 6 hours or<br>Two inhalations 15 to 30 minutes before exercise  |
| <b>How Supplied</b>  | Dry powder inhaler in boxes of one  |
| <b>Storage</b>   | Room temperature (between 15° and 25°C; 59° and 77°F)   |

## APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

### B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on November 13, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.<sup>2</sup>

| <b>Table 3: FAERS Search Strategy</b> |   |
|---------------------------------------|---|
| <b>Date Range</b>                     | <b>May 16, 2014 to November 13, 2014<sup>1</sup></b>  |
| <b>Product</b>                        | <b>ProAir HFA</b>   |
| <b>Event (MedDRA Terms)</b>           | <b>Medication Errors [HLGT]<br/>Product Packaging Issues [HLT]<br/>Product Label Issues [HLT]<br/>Product Quality Issues (NEC)[HLT]</b> |

### B.2 Results

Our search retrieved 54 cases; none of the cases were evaluated further as they described lack of therapeutic effect, labeled adverse reactions, and product complaints. None of the cases retrieved described a medication error related to label and labeling.

### B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

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<sup>2</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

<sup>1</sup> Owens L. Proprietary Name Review for ProAir RespiClick (NDA 205636). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 07 16. 25 p. Panorama No.: 2014-17311

## 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,<sup>2</sup> along with postmarket medication error data, we reviewed the following ProAir RespiClick labels and labeling submitted by Teva Respiratory LLC on May 5, 2014.

- Container label
- Carton labeling
- Foil label
- Instructions for Use (no image attached)
- Full Prescribing Information (no image attached)

### G.2 Label and Labeling Images



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

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/s/  
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LISSA C OWENS  
12/10/2014

KENDRA C WORTHY  
12/10/2014

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

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

**Application:** [NDA 205636](#)

**Application Type:** [New NDA](#)

**Name of Drug/Dosage Form:** [ProAir Respi-Click \(albuterol sulfate\) powder for inhalation](#)

**Applicant:** [Teva Branded Pharmaceuticals R&D, Inc.](#)

**Receipt Date:** [May 05, 2014](#)

**Goal Date:** [March 05, 2015](#)

### **1. Regulatory History and Applicant's Main Proposals**

This is a 505(b)(2) application that relies on [ProAir HFA \(albuterol sulfate\) NDA 21457](#) and [Proventil HFA - NDA 20503](#), [Proventil CFC – NDA 17559](#), and [Proventil Tablets – NDA 17853 \(Withdrawn\)](#).

### **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 for Prescribing Information (SRPI)" checklist (see the Appendix).

### **3. Conclusions/Recommendations**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by [July 28, 2014](#). The resubmitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### 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:**

- YES** 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). A horizontal line must separate the TOC from the FPI.

**Comment:**

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:** *The horizontal lines do not extend over the entire width of the column*

- NO** 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 A for a sample tool illustrating white space in HL.

**Comment:** *There is no white space present before each major heading in HL*

- 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. Section headings must be presented in the following order in HL:

| Section                           | Required/Optional |
|-----------------------------------|-------------------|
| • Highlights Heading              | Required          |
| • Highlights Limitation Statement | Required          |
| • Product Title                   | Required          |

## Selected Requirements of Prescribing Information

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

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

*Comment:*

### HIGHLIGHTS DETAILS

#### Highlights Heading

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

*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 in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

*Comment:*

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

*Comment:*

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

## Selected Requirements of Prescribing Information

### Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

### Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

### Comment:

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

### Comment:

- N/A** 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) --- 9/2013”.

### Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

### Comment:

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

### Comment:

### Contraindications in Highlights

**NO**

## Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

*Comment:* Each contraindication should be bulleted.

### Adverse Reactions in Highlights

- YES** 22. 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) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

*Comment:*

### Patient Counseling Information Statement in Highlights

- YES** 23. 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**”

If a product **has** 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** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

*Comment:*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

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

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. 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:*
- N/A** 27. The same heading 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** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. 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 (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. 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.

|  |
|--|
| <b>BOXED WARNING</b>   |
| <b>1 INDICATIONS AND USAGE</b>                                   |
| <b>2 DOSAGE AND ADMINISTRATION</b>                               |
| <b>3 DOSAGE FORMS AND STRENGTHS</b>                              |
| <b>4 CONTRAINDICATIONS</b>                                       |
| <b>5 WARNINGS AND PRECAUTIONS</b>                                |
| <b>6 ADVERSE REACTIONS</b>                                       |
| <b>7 DRUG INTERACTIONS</b>                                       |
| <b>8 USE IN SPECIFIC POPULATIONS</b>                             |
| <b>8.1 Pregnancy</b>   |
| <b>8.2 Labor and Delivery</b>                                    |
| <b>8.3 Nursing Mothers</b>                                       |
| <b>8.4 Pediatric Use</b>   |
| <b>8.5 Geriatric Use</b>   |
| <b>9 DRUG ABUSE AND DEPENDENCE</b>                               |
| <b>9.1 Controlled Substance</b>                                  |
| <b>9.2 Abuse</b>   |
| <b>9.3 Dependence</b>  |
| <b>10 OVERDOSAGE</b>   |
| <b>11 DESCRIPTION</b>  |
| <b>12 CLINICAL PHARMACOLOGY</b>                                  |
| <b>12.1 Mechanism of Action</b>                                  |
| <b>12.2 Pharmacodynamics</b>                                     |
| <b>12.3 Pharmacokinetics</b>                                     |
| <b>12.4 Microbiology (by guidance)</b>                           |
| <b>12.5 Pharmacogenomics (by guidance)</b>                       |
| <b>13 NONCLINICAL TOXICOLOGY</b>                                 |
| <b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b> |
| <b>13.2 Animal Toxicology and/or Pharmacology</b>                |
| <b>14 CLINICAL STUDIES</b>                                       |
| <b>15 REFERENCES</b>   |
| <b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>                      |
| <b>17 PATIENT COUNSELING INFORMATION</b>                         |

**Comment:**

- YES** 33. 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)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

*Comment:*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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:*

- NO** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), 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:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

**YES**

## Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) 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:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

#### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

#### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

#### DOSAGE AND ADMINISTRATION

- [text]
- [text]

#### DOSAGE FORMS AND STRENGTHS

[text]

#### CONTRAINDICATIONS

- [text]
- [text]

#### WARNINGS AND PRECAUTIONS

- [text]
- [text]

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- [text]
- [text]

#### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

#### 6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

#### 7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 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

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

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

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/s/  
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LEILA P HANN  
07/07/2014

## 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 # 205636<br>BLA#   | NDA Supplement #:S-<br>BLA Supplement #  | Efficacy Supplement Type SE-          |
| Proprietary Name: ProAir RespiClick<br>Established/Proper Name: albuterol sulfate<br>Dosage Form: dry powder for inhalation<br>Strengths: 90 mcg   |  |                                       |
| Applicant: Teva Branded Pharmaceuticals R&D, Inc.<br>Agent for Applicant (if applicable):  |  |                                       |
| Date of Application: May 05, 2014<br>Date of Receipt: May 05, 2014<br>Date clock started after UN:   |  |                                       |
| PDUFA Goal Date: March 05, 2015  |  | Action Goal Date (if different):      |
| Filing Date: July 05, 2015   |  | Date of Filing Meeting: June 04, 2014 |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) 3   |  |                                       |
| Proposed indication(s): Treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease; Prevention of exercise-induced bronchospasm in patients 12 years of age and older  |  |                                       |
| Type of Original NDA:<br>AND (if applicable)<br>Type of NDA Supplement:<br><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i><br><a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> . | <input type="checkbox"/> 505(b)(1)<br><input checked="" type="checkbox"/> 505(b)(2)<br><input type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2)  |                                       |
| Type of BLA<br><i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>   | <input type="checkbox"/> 351(a)<br><input type="checkbox"/> 351(k)   |                                       |
| Review Classification:<br><br><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i><br><br><i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>                   | <input checked="" type="checkbox"/> Standard<br><input type="checkbox"/> Priority<br><br><input type="checkbox"/> Tropical Disease Priority Review Voucher submitted<br><input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted  |                                       |
| Resubmission after withdrawal? <input type="checkbox"/>  | Resubmission after refuse to file? <input type="checkbox"/>  |                                       |
| Part 3 Combination Product? <input type="checkbox"/><br><br><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>   | <input type="checkbox"/> Convenience kit/Co-package<br><input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.)<br><input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.)<br><input type="checkbox"/> Device coated/impregnated/combined with drug<br><input type="checkbox"/> Device coated/impregnated/combined with biologic<br><input type="checkbox"/> Separate products requiring cross-labeling<br><input type="checkbox"/> Drug/Biologic<br><input type="checkbox"/> Possible combination based on cross-labeling of separate products<br><input type="checkbox"/> Other (drug/device/biological product) |                                       |

|   |  |                          |                          |                |
|---|--|--------------------------|--------------------------|----------------|
| <input type="checkbox"/> Fast Track Designation<br><input type="checkbox"/> Breakthrough Therapy Designation<br><i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i><br><input type="checkbox"/> Rolling Review<br><input type="checkbox"/> Orphan Designation<br><br><input type="checkbox"/> Rx-to-OTC switch, Full<br><input type="checkbox"/> Rx-to-OTC switch, Partial<br><input type="checkbox"/> Direct-to-OTC<br><br>Other:  | <input type="checkbox"/> PMC response<br><input type="checkbox"/> PMR response:<br><input type="checkbox"/> FDAAA [505(o)]<br><input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]<br><input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)<br><input type="checkbox"/> 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): 104532   |  |                          |                          |                |
| <b>Goal Dates/Product Names/Classification Properties</b>   | <b>YES</b>   | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| PDUFA and Action Goal dates correct in tracking system?<br><br><i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>  | X  | <input type="checkbox"/> |                          |                |
| Are the proprietary, established/proper, and applicant names correct in tracking system?<br><br><i>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 tracking system.</i>   | X  | <input type="checkbox"/> |                          |                |
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i><br><br><i>If no, ask the document room staff to make the appropriate entries.</i> | X  | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <b>Application Integrity Policy</b>   | <b>YES</b>   | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>  | <input type="checkbox"/>   | X                        |                          |                |
| <b>If yes, explain in comment column.</b>   |  |                          |                          |                |
| <b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>  | <input type="checkbox"/>   | <input type="checkbox"/> |                          |                |
| <b>User Fees</b>  | <b>YES</b>   | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| Is Form 3397 (User Fee Cover Sheet) included with authorized signature?   | X  | <input type="checkbox"/> |                          |                |

|   |           |   |           |                          |                |
|---|-----------|---|-----------|--------------------------|----------------|
| <b>User Fee Status</b><br><br><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. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>   |           | <b>Payment for this application:</b><br><br><input checked="" type="checkbox"/> Paid April 01, 2014<br><input type="checkbox"/> Exempt (orphan, government)<br><input type="checkbox"/> Waived (e.g., small business, public health)<br><input type="checkbox"/> 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. Send UN letter and contact the user fee staff.</i>   |           | <b>Payment of other user fees:</b><br><br><input checked="" type="checkbox"/> Not in arrears<br><input type="checkbox"/> In arrears   |           |                          |                |
| <b>505(b)(2)</b>  |           | <b>YES</b>  | <b>NO</b> | <b>NA</b>                | <b>Comment</b> |
| <b>(NDAs/NDA Efficacy Supplements only)</b>   |           |   |           |                          |                |
| Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?  |           | <input type="checkbox"/>  | X         | <input type="checkbox"/> |                |
| 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)].   |           | <input type="checkbox"/>  | X         | <input type="checkbox"/> |                |
| 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)]?   |           | <input type="checkbox"/>  | X         | <input type="checkbox"/> |                |
| <i>If you answered yes to any of the above 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</i>   |           |   |           |                          |                |
| Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?   |           | <input type="checkbox"/>  | X         | <input type="checkbox"/> |                |
| <b>Check the Electronic Orange Book at:</b><br><a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>  |           |   |           |                          |                |
| <b>If yes, please list below:</b>   |           |   |           |                          |                |
| Application No.   | Drug Name | Exclusivity Code  |           | Exclusivity Expiration   |                |
|   |           |   |           |                          |                |
|   |           |   |           |                          |                |
|   |           |   |           |                          |                |
| <i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, 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, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i> |           |   |           |                          |                |
| <b>Exclusivity</b>  |           | <b>YES</b>  | <b>NO</b> | <b>NA</b>                | <b>Comment</b> |
| Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug</b>   |           | <input type="checkbox"/>  | X         |                          |                |

|  |                          |                          |                          |  |
|--|--------------------------|--------------------------|--------------------------|--|
| <b>Designations and Approvals list at:</b><br><a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>  |                          |                          |                          |  |
| <b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?<br><br><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>   | <input type="checkbox"/> | <input type="checkbox"/> | X                        |  |
| Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)<br><br><b>If yes, # years requested:</b><br><br><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>  | <input type="checkbox"/> | X                        | <input type="checkbox"/> |  |
| Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only)?   | <input type="checkbox"/> | X                        | <input type="checkbox"/> |  |
| <b>If yes</b> , 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)?<br><br><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>   | <input type="checkbox"/> | <input type="checkbox"/> | X                        |  |
| <b>For BLAs:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?<br><br><i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i><br><br><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> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |  |

| <b>Format and Content</b>  |   |
|--|---|
| <i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>            | <input type="checkbox"/> All paper (except for COL)<br>X All electronic<br><input type="checkbox"/> Mixed (paper/electronic)<br><br>X CTD<br><input type="checkbox"/> Non-CTD<br><input type="checkbox"/> Mixed (CTD/non-CTD) |
| <b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format? |   |

| <b>Overall Format/Content</b>   | <b>YES</b>               | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
|---|--------------------------|--------------------------|--------------------------|----------------|
| <b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup><br><b>If not</b> , explain (e.g., waiver granted).   | X                        | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <b>Index:</b> Does the submission contain an accurate comprehensive index?  | X                        | <input type="checkbox"/> |                          |                |
| 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:<br><br>X legible<br>X English (or translated into English)<br>X pagination<br>X navigable hyperlinks (electronic submissions only)<br><br><b>If no</b> , explain.   | X                        | <input type="checkbox"/> |                          |                |
| <b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?<br><br><b>If yes</b> , BLA #   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                |
|   |                          |                          |                          |                |
|   |                          |                          |                          |                |
|   |                          |                          |                          |                |
|   |                          |                          |                          |                |
|   |                          |                          |                          |                |
| <b>Forms and Certifications</b>   |                          |                          |                          |                |
| <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), 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> |                          |                          |                          |                |
| <b>Application Form</b>   | <b>YES</b>               | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?<br><br><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>  | X                        | <input type="checkbox"/> |                          |                |
| Are all establishments and their registration numbers listed on the form/attached to the form?  | X                        | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <b>Patent Information</b><br>(NDAs/NDA efficacy supplements only)   | <b>YES</b>               | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?   | X                        | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <b>Financial Disclosure</b>   | <b>YES</b>               | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| Are financial disclosure forms FDA 3454 and/or 3455   | X                        | <input type="checkbox"/> |                          |                |

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

|  |                          |                          |                          |  |
|--|--------------------------|--------------------------|--------------------------|--|
| included with authorized signature per 21 CFR 54.4(a)(1) and (3)?<br><br><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i><br><br><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>   |                          |                          |                          |  |
| <b>Clinical Trials Database</b>  | <b>YES</b>               | <b>NO</b>                | <b>NA</b>                | <b>Comment</b>   |
| Is form FDA 3674 included with authorized signature?<br><br><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i><br><br><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>   | X                        | <input type="checkbox"/> |                          |  |
| <b>Debarment Certification</b>   | <b>YES</b>               | <b>NO</b>                | <b>NA</b>                | <b>Comment</b>   |
| Is a correctly worded Debarment Certification included with authorized signature?<br><br><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><br><br><i>Note: Debarment Certification should use wording in FD&amp;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> | X                        | <input type="checkbox"/> | <input type="checkbox"/> | Does is have to be EXACT?<br>Applicant wording:<br>On behalf of TEVA Branded Pharmaceutical Products R&D, Inc., the applicant, I hereby certify, pursuant to Section 306(k) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 335a(k)) as amended by the Generic Drug Enforcement Act of 1992, that it did not and will not use in any capacity the services of any person who has been debarred pursuant to Section 306 of the Federal Food, Drug, and Cosmetic Act, in connection with this application. |
| <b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>   | <b>YES</b>               | <b>NO</b>                | <b>NA</b>                | <b>Comment</b>   |
| <b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?<br><br><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><br><br><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>   | <input type="checkbox"/> | <input type="checkbox"/> | X                        |  |
| <b>Controlled Substance/Product with Abuse Potential</b>   | <b>YES</b>               | <b>NO</b>                | <b>NA</b>                | <b>Comment</b>   |

|   |                          |                          |                          |                |
|---|--------------------------|--------------------------|--------------------------|----------------|
| <u>For NMEs:</u><br>Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?<br><br><i>If yes, date consult sent to the Controlled Substance Staff:</i><br><br><u>For non-NMEs:</u><br>Date of consult sent to Controlled Substance Staff :   | <input type="checkbox"/> | <input type="checkbox"/> | X                        |                |
| <b>Pediatrics</b>   | <b>YES</b>               | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| <u>PREA</u><br><br>Does the application trigger PREA?<br><br><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i><br><br><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i> | X                        | <input type="checkbox"/> |                          |                |
| <b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?   | <input type="checkbox"/> | X                        | <input type="checkbox"/> |                |
| <b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?<br><br><i>If no, request in 74-day letter</i>   | X                        | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?<br><br><i>If no, request in 74-day letter</i>  | X                        | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <u>BPCA (NDAs/NDA efficacy supplements only):</u><br><br>Is this submission a complete response to a pediatric Written Request?<br><br><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>  | <input type="checkbox"/> | X                        |                          |                |
| <b>Proprietary Name</b>   | <b>YES</b>               | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| Is a proposed proprietary name submitted?<br><br><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>   | X                        | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <b>REMS</b>   | <b>YES</b>               | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

|  |  |                          |                          |                |
|--|--|--------------------------|--------------------------|----------------|
| Is a REMS submitted?<br><br><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>   | <input type="checkbox"/>   | X                        | <input type="checkbox"/> |                |
| <b>Prescription Labeling</b>   | <input type="checkbox"/> <b>Not applicable</b>   |                          |                          |                |
| Check all types of labeling submitted.   | <input checked="" type="checkbox"/> Package Insert (PI)<br><input checked="" type="checkbox"/> Patient Package Insert (PPI)<br><input checked="" type="checkbox"/> Instructions for Use (IFU)<br><input type="checkbox"/> Medication Guide (MedGuide)<br><input checked="" type="checkbox"/> Carton labels<br><input checked="" type="checkbox"/> Immediate container labels<br><input type="checkbox"/> Diluent<br><input type="checkbox"/> Other (specify) |                          |                          |                |
|  | <b>YES</b>   | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| Is Electronic Content of Labeling (COL) submitted in SPL format?<br><br><i>If no, request applicant to submit SPL before the filing date.</i>  | X  | <input type="checkbox"/> |                          |                |
| Is the PI submitted in PLR format? <sup>4</sup>  | X  | <input type="checkbox"/> |                          |                |
| <b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?<br><br><i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i> | <input type="checkbox"/>   | <input type="checkbox"/> | X                        |                |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?  | X  | <input type="checkbox"/> | <input type="checkbox"/> |                |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)  | X  | <input type="checkbox"/> | <input type="checkbox"/> |                |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?   | X  | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <b>OTC Labeling</b>  | <b>X Not Applicable</b>  |                          |                          |                |
| Check all types of labeling submitted.   | <input type="checkbox"/> Outer carton label<br><input type="checkbox"/> Immediate container label<br><input type="checkbox"/> Blister card<br><input type="checkbox"/> Blister backing label<br><input type="checkbox"/> Consumer Information Leaflet (CIL)<br><input type="checkbox"/> Physician sample<br><input type="checkbox"/> Consumer sample<br><input type="checkbox"/> Other (specify)   |                          |                          |                |
|  | <b>YES</b>   | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| Is electronic content of labeling (COL) submitted?   | <input type="checkbox"/>   | <input type="checkbox"/> |                          |                |

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

|  |                          |                          |                          |   |
|--|--------------------------|--------------------------|--------------------------|---|
| <i>If no, request in 74-day letter.</i>  |                          |                          |                          |   |
| Are annotated specifications submitted for all stock keeping units (SKUs)?                               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |   |
| <i>If no, request in 74-day letter.</i>  |                          |                          |                          |   |
| If representative labeling is submitted, are all represented SKUs defined?                               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |   |
| <i>If no, request in 74-day letter.</i>  |                          |                          |                          |   |
| All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?                        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |   |
| <b>Other Consults</b>  | <b>YES</b>               | <b>NO</b>                | <b>NA</b>                | <b>Comment</b>  |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) | X                        | <input type="checkbox"/> | <input type="checkbox"/> | DMPP (PLT) 05/22/2014; CDRH – HFS 05/28/2014; CDRH – device facilities 06/24/2014; CDRH – device 06/26/2014 |
| <i>If yes, specify consult(s) and date(s) sent:</i>  |                          |                          |                          |   |
| <b>Meeting Minutes/SPAs</b>  | <b>YES</b>               | <b>NO</b>                | <b>NA</b>                | <b>Comment</b>  |
| End-of Phase 2 meeting(s)<br><b>Date(s):</b> October 05, 2010  | X                        | <input type="checkbox"/> |                          |   |
| <i>If yes, distribute minutes before filing meeting</i>  |                          |                          |                          |   |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?<br><b>Date(s):</b> November 19, 2013                          | X                        | <input type="checkbox"/> |                          |   |
| <i>If yes, distribute minutes before filing meeting</i>  |                          |                          |                          |   |
| Any Special Protocol Assessments (SPAs)?<br><b>Date(s):</b>  | <input type="checkbox"/> | X                        |                          |   |
| <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>                           |                          |                          |                          |   |

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** June 04, 2014

**NDA #:** 205636

**PROPRIETARY NAME:** ProAir RespiClick

**ESTABLISHED/PROPER NAME:** albuterol sulfate

**DOSAGE FORM/STRENGTH:** dry powder for inhalation/ 90mcg

**APPLICANT:** Teva Branded Pharmaceutical R&D, Inc.

**PROPOSED INDICATION(S):** Treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease; Prevention of exercise-induced bronchospasm in patients 12 years of age and older

**BACKGROUND:**

**REVIEW TEAM:**

| Discipline/Organization                                     | Names           |                 | Present at filing meeting? (Y or N) |
|---|-----------------|-----------------|-------------------------------------|
| Regulatory Project Management                               | RPM:            | Leila P. Hann   | Y                                   |
|   | CPMS/TL:        | Sandy Barnes    | N                                   |
| Cross-Discipline Team Leader (CDTL)                         | Nikolay Nikolov |                 | Y                                   |
| Clinical  | Reviewer:       | Keith Hull      | Y                                   |
|   | TL:             | Nikolay Nikolov | Y                                   |
| Social Scientist Review ( <i>for OTC products</i> )         | Reviewer:       |                 |                                     |
|   | TL:             |                 |                                     |
| OTC Labeling Review ( <i>for OTC products</i> )             | Reviewer:       |                 |                                     |
|   | TL:             |                 |                                     |
| Clinical Microbiology ( <i>for antimicrobial products</i> ) | Reviewer:       |                 |                                     |
|   | TL:             |                 |                                     |

|   |           |               |   |
|---|-----------|---------------|---|
| Clinical Pharmacology   | Reviewer: | Yunzhao Ren   | Y |
|   | TL:       | Satjit Brar   | Y |
| Biostatistics   | Reviewer: | Robert Abugov | Y |
|   | TL:       | David Petullo | Y |
| Nonclinical<br>(Pharmacology/Toxicology)  | Reviewer: | Nikunj Patel  | Y |
|   | TL:       | Marcie Wood   | Y |
| Statistics (carcinogenicity)  | Reviewer: |               |   |
|   | TL:       |               |   |
| Immunogenicity (assay/assay<br>validation) ( <i>for BLAs/BLA efficacy<br/>supplements</i> ) | Reviewer: |               |   |
|   | TL:       |               |   |
| Product Quality (CMC)   | Reviewer: | Yong Hu       | Y |
|   | TL:       | Craig Bertha  | Y |
| Quality Microbiology ( <i>for sterile<br/>products</i> )                                    | Reviewer: |               |   |
|   | TL:       |               |   |
| CMC Labeling Review   | Reviewer: |               |   |
|   | TL:       |               |   |
| Facility Review/Inspection  | Reviewer: | Linda Ng      | Y |
|   | TL:       |               |   |
| OSE/DMEPA (proprietary name)  | Reviewer: |               |   |
|   | TL:       |               |   |
| OSE/DRISK (REMS)  | Reviewer: | Robert Pratt  | N |
|   | TL:       |               |   |
| OC/OSI/DSC/PMSB (REMS)  | Reviewer: |               |   |
|   | TL:       |               |   |

|                                  |                                     |  |  |
|----------------------------------|-------------------------------------|--|--|
| Bioresearch Monitoring (OSI)     | Reviewer:                           |  |  |
|                                  | TL:                                 |  |  |
| Controlled Substance Staff (CSS) | Reviewer:                           |  |  |
|                                  | TL:                                 |  |  |
| Other reviewers                  |                                     |  |  |
| Other attendees                  | Badrul Chowdhury<br>Nichelle Rashid |  |  |

**FILING MEETING DISCUSSION:**

|  |   |
|--|---|
| <p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p> | <input type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO<br><br><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO<br><br>BE study |
| <ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>  | <input type="checkbox"/> Not Applicable   |
| <p><b>CLINICAL</b></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter            |
| <ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |

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| <ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><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></li> </ul> | <input type="checkbox"/> YES<br>Date if known:<br><input checked="" type="checkbox"/> NO<br><input type="checkbox"/> To be determined<br><br>Reason:   |
| <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>  | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>  | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>   | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO   |
| <p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |

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| <p><b>NONCLINICAL<br/>(PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>  | <p><input type="checkbox"/> Not Applicable<br/> <input checked="" type="checkbox"/> FILE<br/> <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>                 |
| <p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>  | <p><input checked="" type="checkbox"/> Not Applicable<br/> <input type="checkbox"/> FILE<br/> <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>                 |
| <p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>  | <p><input type="checkbox"/> Not Applicable<br/> <input checked="" type="checkbox"/> FILE<br/> <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>      |
| <p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p> | <p><input checked="" type="checkbox"/> YES<br/> <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES<br/> <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES<br/> <input type="checkbox"/> NO</p> |
| <p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>  | <p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES<br/> <input type="checkbox"/> NO</p>  |
| <p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>   | <p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES<br/> <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES<br/> <input type="checkbox"/> NO</p>                       |

|  |   |
|--|---|
| <p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>   | <p>X Not Applicable<br/> <input type="checkbox"/> FILE<br/> <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p> |
| <p><b><u>CMC Labeling Review</u></b></p> <p>Comments:</p>  | <p><input type="checkbox"/> Review issues for 74-day letter</p>   |
| <p><b>APPLICATIONS IN THE PROGRAM (PDUFA V)<br/>(NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• 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?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul> | <p>X N/A</p> <p><input type="checkbox"/> YES<br/> <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES<br/> <input type="checkbox"/> NO</p>                  |
| <ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>  |   |
| <ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>  | <p><input type="checkbox"/> YES<br/> <input type="checkbox"/> NO</p>  |
| <ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>   | <p><input type="checkbox"/> YES<br/> <input type="checkbox"/> NO</p>  |
| <ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>   | <p><input type="checkbox"/> YES<br/> <input type="checkbox"/> NO</p>  |
| <b>REGULATORY PROJECT MANAGEMENT</b>   |   |
| <b>Signatory Authority:</b>  |   |

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V):

**21<sup>st</sup> Century Review Milestones (see attached)** (listing review milestones in this document is optional):

**Comments:**

**REGULATORY CONCLUSIONS/DEFICIENCIES**

|                          |   |
|--------------------------|---|
| <input type="checkbox"/> | The application is unsuitable for filing. Explain why:  |
| X                        | <p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p>X Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p>X Standard Review</p> <p><input type="checkbox"/> Priority Review</p> |

**ACTIONS ITEMS**

|                          |   |
|--------------------------|---|
| X                        | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).  |
| <input type="checkbox"/> | If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).  |
| <input type="checkbox"/> | 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.   |
| <input type="checkbox"/> | BLA/BLA supplements: If filed, send 60-day filing letter  |
| <input type="checkbox"/> | <p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul> |
| X                        | Send review issues/no review issues by day 74   |
| X                        | Conduct a PLR format labeling review and include labeling issues in the 74-day letter   |
| <input type="checkbox"/> | Update the PDUFA V DARRTS page (for NME NDAs in the Program)  |
| <input type="checkbox"/> | BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and   |

|                          |  |
|--------------------------|--|
|                          | the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:<br><a href="http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ] |
| <input type="checkbox"/> | Other  |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LEILA P HANN  
06/30/2014