

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207921Orig1s000**

**OTHER REVIEW(S)**

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

| <b>Application Information</b>                                                                                                                                     |                                  |                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|------------------------------|
| NDA # 207921                                                                                                                                                       | NDA Supplement #: S-             | Efficacy Supplement Type SE- |
| Proprietary Name: QVAR RediHaler<br>Established/Proper Name: beclomethasone dipropionate<br>Dosage Form: Inhalation Aerosol<br>Strengths: 40 and 80 mcg/ actuation |                                  |                              |
| Applicant: Norton (Waterford) Ltd. A wholly-owned subsidiary of Teva Pharmaceutical Industries Ltd.                                                                |                                  |                              |
| Date of Receipt: October 3, 2016                                                                                                                                   |                                  |                              |
| PDUFA Goal Date: August 3, 2017                                                                                                                                    | Action Goal Date (if different): |                              |
| RPM: Laura Musse                                                                                                                                                   |                                  |                              |
| Proposed Indication(s): Maintenance treatment of asthma as prophylactic therapy in patients 4 years of age 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.)*

|                                                                                                    |                                                                                                   |
|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Published literature, BECLOVENT,<br>(beclomethasone dipropionate)<br>Inhalation Aerosol NDA 018153 | Labeling text and human<br>pharmacokinetics and bioavailability<br>of beclomethasone dipropionate |
|                                                                                                    |                                                                                                   |

\*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.](#)

|  |  |  |  |
|--|--|--|--|
|  |  |  |  |
|  |  |  |  |

One pharmacokinetic, Phase 1 study (BDB-AS-101) was conducted to characterize the pharmacokinetics of the beclomethasone dipropionate BAI and to evaluate the relative bioavailability of 17-BMP and beclomethasone dipropionate from beclomethasone dipropionate BAI to a well-characterized marketed product, QVAR Inhalation Aerosol (beclomethasone dipropionate MDI). As QVAR is owned by the same parent company as the applicant holder for QVAR redihaler, this is a cross reference and does not require a bridge for 505(b)(2) regulatory purposes. QVAR was approved as a 505(b)(2) NDA that relied upon the listed drug BECLOVENT which is no longer marketed. The bridge to Beclovent was established when QVAR was approved and does not need to be re-established. The proposed QVAR redihaler product is cross referencing QVAR (for nonclinical) as both NDAs are owned by the same parent company.

[Noted: The applicant submitted a clinical study to this QVAR redihaler NDA and the clinical review did not rely upon any published literature. The applicant also cites QNASL as relied upon although this NDA is also owned by this applicant and the nonclinical studies submitted to the QNASL NDA were not reviewed under the QNASL NDA. Those nonclinical studies were reviewed under the QVAR NDA and cross referenced to the QNASL NDA.]

<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 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).*

*BECLOVENT and QVAR*

- (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) |
|---------------------|------------|------------------------------------------------------|
| BECLOVENT           | NDA 018153 | 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:

- 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: BECLOVENT (NDA 18153)

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 breath actuated, primeless inhaler device. The listed drugs are press and breathe inhalation aerosols.

*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): Vanceril, and Vanceril double strength  
Beclovent and Qvar (identified as listed drugs)

**PATENT CERTIFICATION/STATEMENTS**

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

Listed drug/Patent number(s):

No patents listed  proceed to question #14

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

YES  NO

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

Listed drug/Patent number(s):

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

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): 4,364,923

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):

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

YES  NO

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

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

YES  NO

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

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

Date(s):

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

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

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

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

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**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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LAURA MUSSE  
08/03/2017

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

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

**Application:** NDA 207921

**Application Type:** New NDA

**Drug Name(s)/Dosage Form(s):** QVAR RediHaler (beclomethasone dipropionate) Inhalation Aerosol

**Applicant:** Norton (Waterford)

**Receipt Date:** October 3, 2016

**Goal Date:** August 3, 2017

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

Norton (Waterford) has developed a breath-actuated version of beclomethasone dipropionate inhalation aerosol. The device ensures that actuation of the metered-dose valve occurs automatically when the patient inhales. The approved proprietary name is QVAR Redihaler.

### **2. Review of the Prescribing Information**

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

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

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

# Selected Requirements of Prescribing Information

## 4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-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 for a sample tool illustrating Highlights format.

#### HIGHLIGHTS GENERAL FORMAT

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

Comment:

- 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), **and**
  - TOC from the Full Prescribing Information (FPI).

Comment:

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

Comment:

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

Comment:

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

Comment:

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

| Heading              | Required/Optional |
|----------------------|-------------------|
| • Highlights Heading | Required          |

## Selected Requirements of Prescribing Information

|                                                   |                                                       |
|---------------------------------------------------|-------------------------------------------------------|
| • <b>Highlights Limitation Statement</b>          | Required                                              |
| • <b>Product Title</b>                            | Required                                              |
| • <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 five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

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

**Comment:**

#### Highlights Limitation Statement

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

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

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

**Comment:**

#### Boxed Warning (BW) in Highlights

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

**Comment:**

- YES** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term

## Selected Requirements of Prescribing Information

“WARNING” and not “WARNINGS” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

**Comment:**

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

**Comment:**

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

**Comment:**

### Recent Major Changes (RMC) in Highlights

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

**Comment:**

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

**Comment:**

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

**Comment:**

### Dosage Forms and Strengths in Highlights

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

**Comment:**

### Contraindications in Highlights

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

**Comment:**

## Selected Requirements of Prescribing Information

### Adverse Reactions in Highlights

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

*Comment:*

### Patient Counseling Information Statement in Highlights

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

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

- See 17 for **PATIENT COUNSELING INFORMATION**

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

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

*Comment:*

### Revision Date in Highlights

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

*Comment:* *Date will be added upon approval*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

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

- YES** 24. The TOC should be in a two-column format.  
*Comment:*
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].  
*Comment:*
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS\***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

|                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------|
| <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>                                                                                   |
| 8.1 Pregnancy                                                                                                          |
| 8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery") |
| 8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")          |
| 8.4 Pediatric Use                                                                                                      |
| 8.5 Geriatric Use                                                                                                      |
| <b>9 DRUG ABUSE AND DEPENDENCE</b>                                                                                     |
| 9.1 Controlled Substance                                                                                               |
| 9.2 Abuse                                                                                                              |
| 9.3 Dependence                                                                                                         |
| <b>10 OVERDOSAGE</b>                                                                                                   |
| <b>11 DESCRIPTION</b>                                                                                                  |
| <b>12 CLINICAL PHARMACOLOGY</b>                                                                                        |
| 12.1 Mechanism of Action                                                                                               |
| 12.2 Pharmacodynamics                                                                                                  |
| 12.3 Pharmacokinetics                                                                                                  |
| 12.4 Microbiology (by guidance)                                                                                        |
| 12.5 Pharmacogenomics (by guidance)                                                                                    |
| <b>13 NONCLINICAL TOXICOLOGY</b>                                                                                       |
| 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility                                                              |
| 13.2 Animal Toxicology and/or Pharmacology                                                                             |
| <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** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

**Comment:**

## Selected Requirements of Prescribing Information

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

Comment:

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

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

Comment:

#### BOXED WARNING Section in the FPI

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

Comment:

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

Comment:

#### CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

#### ADVERSE REACTIONS Section in the FPI

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

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

Comment:

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

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

Comment:

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

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

**Comment:**

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

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix: Highlights and Table of Contents Format

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

#### WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

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

#### RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y  
Section Title, Subsection Title (x.x) M/201Y

#### INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

#### DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

#### DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

#### CONTRAINDICATIONS

- Text (4)
- Text (4)

#### WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

#### ADVERSE REACTIONS

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

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

#### DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

#### USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

### FULL PRESCRIBING INFORMATION: CONTENTS\*

#### WARNING: TITLE OF WARNING

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

#### 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

#### 7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

#### 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 Subsection Title

14.2 Subsection Title

#### 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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**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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LAURA MUSSE  
07/24/2017

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## HUMAN FACTORS REPORT, LABEL, LABELING, AND PACKAGING 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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|                                              |                                                                                                                        |
|----------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| <b>Date of This Review:</b>                  | July 11, 2017                                                                                                          |
| <b>Requesting Office or Division:</b>        | Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)                                                      |
| <b>Application Type and Number:</b>          | NDA 207921                                                                                                             |
| <b>Product Type:</b>                         | Single-Ingredient Drug Device Combination Product                                                                      |
| <b>Drug Constituent Name and Strength</b>    | Qvar RediHaler (Beclomethasone Dipropionate)<br>Breath-actuated Inhalation Aerosol<br>40 mcg and 80 mcg per inhalation |
| <b>Device Constituent:</b>                   | Inhaler                                                                                                                |
| <b>Rx or OTC:</b>                            | Rx                                                                                                                     |
| <b>Applicant/Sponsor Name:</b>               | Teva Pharmaceuticals                                                                                                   |
| <b>Submission Date:</b>                      | October 1, 2016 and June 15, 2017                                                                                      |
| <b>OSE RCM #:</b>                            | 2016-2357 and 2016-2358                                                                                                |
| <b>Safety Evaluator:</b>                     | Lissa C. Owens, PharmD                                                                                                 |
| <b>Team Leader:</b>                          | Sarah K. Vee, PharmD                                                                                                   |
| <b>Associate Director for Human Factors:</b> | QuynhNhu Nguyen, MS                                                                                                    |

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## 1 REASON FOR REVIEW

This review responds to a request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to review the Human Factors (HF) validation study report, proposed container label, carton labeling, instructions for use (IFU), and Prescribing Information (PI) submitted on October 1, 2016 and June 15, 2017 as a 505(b)(2) submission under NDA 207921. As part of the approval process for Qvar RediHaler, we reviewed the HF validation study report and proposed labeling for any vulnerability from a medication error perspective.

## 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<br/>(for Methods and Results)</b> |
| Product Information/Prescribing Information                             | A                                                     |
| Previous DMEPA Reviews                                                  | B-N/A                                                 |
| Human Factors Study                                                     | C                                                     |
| ISMP Newsletters                                                        | D-N/A                                                 |
| FDA Adverse Event Reporting System (FAERS)*                             | E-N/A                                                 |
| Other                                                                   | F                                                     |
| Labels and Labeling                                                     | G                                                     |

N/A=not applicable for this review

\*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

### 3.1 HUMAN FACTORS VALIDATION STUDY

Teva Pharmaceuticals performed a HF validation study to evaluate the safe and effective use of the proposed Qvar RediHaler breath-actuated inhaler. DMEPA provided recommendations regarding the HF validation study and protocol under IND 114865<sup>ab</sup>. A total of 91 participants (16 MDI-naïve adults, 15 MDI-experienced adults, 15 MDI-naïve adolescents, 15 MDI-experienced adolescents, 15 MDI-naïve pediatrics, and 15 MDI-experienced pediatrics) participated in the HF validation study. The study evaluated Use Task 1-IFU use optional, Use Task 2-IFU use required, Use Task 3-Inhaler end of content, and Use Task 4-Cap left open. Each task consisted of additional sub-tasks that were also evaluated.

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<sup>a</sup> <http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af802a0379>

<sup>b</sup> <http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af802f2319>

On June 12, 2017, we sent an information request (IR) (See Appendix F) to Teva for further clarification regarding the detailed description of all errors, close calls, and instances of test administrator assistance observed in each of the four tasks and associated subtasks and for clarification regarding the proposed labeling. Teva responded on June 15, 2017 and we reviewed the response in addition to the HF validation study report. Use errors, including test administrator assistance, close calls, and user difficulties are evaluated below.

### High level Task Results

**Table 20: Task Performance Summary**

| Task # | Task priority | Task description       | Number of participants who attempted the task | Number of participants who did not successfully complete task | Safety-related task pass rate | Safety-related failure type          |                                        |
|--------|---------------|------------------------|-----------------------------------------------|---------------------------------------------------------------|-------------------------------|--------------------------------------|----------------------------------------|
|        |               |                        |                                               |                                                               |                               | Total number of use errors committed | Total instances of test admin. assists |
| 1      | 1             | IFU use optional       | 91                                            | 15                                                            | n = 76 (83.5%)                | 18                                   | 1                                      |
| 2      | 2             | IFU use required       | 91                                            | 6                                                             | n = 84 (92.3%)                | 6                                    | 0                                      |
| 3      | 4             | Inhaler end of content | 91                                            | 0                                                             | n = 91 (100%)                 | 0                                    | 0                                      |
| 4      | 3             | Cap left open          | 91                                            | 5                                                             | n = 86 (94.5%)                | 5                                    | 0                                      |

#### Task 1: IFU use optional

In task 1 participant was instructed to take two inhalations of the medication. They were provided with the IFU but not instructed to use it. Subtasks included opening the white dust cap, breathing out, closing lips around mouthpiece and breathing in deeply (1<sup>st</sup> inhalation), removing the inhaler from the mouth and holding breath for at least 5 seconds, and closing the white dust cap. The above subtasks were then repeated to simulate a 2<sup>nd</sup> inhalation. All participants under task 1 were able to successfully open the white dust cap, breathe out, and remove the inhaler from mouth and hold breath for at least 5 seconds. The following sections focus on the failures, close calls, and use difficulties that were observed for Task 1.

#### Subtask 3: Close lips around mouthpiece and breathe in deeply (1<sup>st</sup> inhalation)

There were five reported use errors that included one test administrator assistance. Four of the use errors resulted from the participant not inhaling sufficiently to actuate the inhaler. Of these four, two participants stated that they were unsure if they had taken the inhalations correctly because they did not have inhaler experience and did not know what to expect when inhaling. These participants were able to self-correct during the second inhalation and successfully complete the task. The third participant did not inhale as they thought that it was a press and breathe inhaler like the inhaler they currently use and therefore missed the dose. The parent

stated that they expected to use the inhaler in the same manner as the participant's current inhaler which is a metered dose inhaler. The root cause was reported as negative transfer. After a review of the IFU, the participant was able to administer a dose.

Lastly, one use error occurred due to test administrator assistance. In this case the participant failed to understand that the inhaler was breath-actuated and attempted to actuate the inhaler by pressing the top without inhaling and therefore failed to actuate the inhaler. The test administrator then directed the participant to read the IFU. The participant read the IFU and inhaled deeply enough to actuate the inhaler and received the dose. The participant had experienced negative transfer as they were used to a press and breathe inhaler with their MDI.

There were no mitigations proposed. After participants referred to or read the instructions (during Task 2), they were able to use the device successfully. Given the chronicity of use for the proposed product, we expect that users will become more familiar with the proper use after repeated use and we do not have any recommendations at this time.

#### Subtask 6: Close white dust cap (after 1<sup>st</sup> inhalation)

There were six use errors, seventeen close calls, and one use difficulty reported in this subtask. We note that not closing the white dust cap after the 1<sup>st</sup> inhalation is not considered a critical task because an adequate dose will still be delivered to patients when a second dose is taken right after the 1<sup>st</sup> dose. In addition, we consulted the medical officer (See Appendix F) and they agreed with Teva that this will not cause harm to the patient. Of the six use errors, root causes included participants was not aware that the cap was required to be closed in order to load the device for the next dose and negative transfer since this feature is unique to the proposed product.

There were seventeen close calls in which participants almost did not close the white cap but were able to self-correct because they did not feel any medication or taste any medication. There was one participant who did not understand the white cap's purpose. The root cause was negative transfer as this was a participant with metered-dose inhaler experience and after reviewing the IFU (without prompting from the administrator) was able to administer the dose successfully.

In the one use difficulty, the participant did not understand that the white cap needed to be closed to load the dose. The patient stated that they had used an inhaler for many years and never had to close the cap in order to load a dose. After reviewing the instructions for use in Task 2 the patient was able to administer both doses without difficulties.

Teva did not propose any mitigations to the labeling or user interface. Although this is not listed as a critical task for in between inhalations, closing the cap after a complete dose (e.g., for next day use) is a critical task. Therefore, labeling changes may help to further mitigate this error and we make recommendations in section 4.1.

### Subtask 6: Did not perform two inhalations

There were eight reported use errors in which participants did not take the prescribed dose of two inhalations. Six of the participants (and/or their parents) misinterpreted the task prompt 'take two inhalations, once per day' and thought they should only take one inhalation. Another participant was unaware that they only took one inhalation and the last participant did not take the second inhalation because they did not like the placebo's taste. We attributed these errors to study artifacts. Therefore, we do not have any recommendations at this time.

### **Task 2: IFU use required**

In task 2 participants were instructed to take two inhalations of the medication and were required to use the IFU for directions. Subtasks included, opening the white dust cap, breathing out, closing lips around the mouthpiece and breathing in deeply (1st inhalation), removing the inhaler from mouth and holding breath for at least 5 seconds, and closing the white dust cap. The above subtasks were then repeated to simulate a 2<sup>nd</sup> inhalation. All participants under task 2 were able to successfully open white dust cap in the 1<sup>st</sup> inhalation, Breathe out, close lips around mouthpiece and breathe in deeply, and remove inhaler from mouth and hold breath for at least 5 seconds. The following sections focus on the failures, close calls, and use difficulties that were observed for Task 2.

### Subtask 5: Close white dust cap (1<sup>st</sup> inhalation)

As previously stated, this task is not considered a critical task because an adequate dose will still be delivered to patients if the cap is not closed in between doses.

There were two use errors in which one participant focused on the illustrations in the IFU rather than the text and the other participant overlooked the step in the IFU because they focused on the bolded text only. Closing in between inhalations is not bolded but closing the cap to reload the inhaler is bolded.

In addition, two participants stated that they realized they need to close the white cap to load the inhaler because they did not detect any medication during the second inhalation. The other participant read steps 1 and 2 and took two inhalations at once. This participant went back, and upon reading step 3 (close white cap to reload inhaler), they realized that they needed to close the cap to reload the inhaler.

There was one participant that experienced user difficulty with understanding the purpose of the white cap. The participant then referred to the IFU and was able to self-correct. The root cause was attributed to negative transfer from metered dose inhaler use. There were no mitigations proposed. Although this is not listed as a critical task for in between inhalations, closing the cap after a complete dose is a critical task. Therefore, labeling changes may help to mitigate this error and we make recommendations in section 4.1.

### Subtask 6: Did not take two inhalations

There were four reported use errors in which participants did not administer the prescribed dose due to misinterpreting the task prompt. Participants were instructed to take two inhalations, once per day and they misunderstood thinking they only needed to take one

inhalation. These errors are due to study artifact and no mitigations are proposed. We do not have any recommendations at this time.

### **Task 3: Inhaler end of content**

In task 3 the participants were provided with two inhalers, one with a dose counter reading of 20 and the other with a dose counter reading of 0 and were asked how many more inhalations were available. Subtasks included viewing the inhaler's dose counter, stating that 20 inhalations remained in the inhaler, and when asked what should be done next, stating that they would obtain a new inhaler. All participants successfully completed all the subtasks under task 3 with no reported errors, close calls, or use difficulties.

### **Task 4: Cap left open**

In task 4 participants were provided with an inhaler with the cap left open and were asked to take two inhalations of the medication. Subtasks included opening the white dust cap, breathing out, closing lips around the mouthpiece and breathing in deeply, removing the inhaler from mouth and holding breath for at least 5 seconds, and closing the white dust cap. All participants under task 4 were able to successfully breathe out, and remove the inhaler from the mouth and hold their breath for at least 5 seconds.

#### **Subtask 1: Close white dust cap**

There were four reported use errors and seven close calls. Unlike the task 1 and 2 in which the two inhalations are taken right after another, not closing the white dust cap before administering the first dose after the cap was left open can be a critical error depending on how long the cap is left open and if it is consistently left open. In two of the errors, the patients corrected after reading the instructions. The other two errors occurred in self-administering pediatric patients and the parents observed the error but did not intervene. However the parents stated that in actual use they would have intervened.

There were seven close calls in which participants almost missed the dose. There were no mitigations proposed; however, labeling changes may help to mitigate this error and we make recommendations in section 4.1.

#### **Subtask 2: Open White dust cap**

There was one use difficulty reported in which the participant believed opening the cap would release the medication rather than load the dose. However, the medication is not released during the opening and closing of the cap and therefore changes to the user-interface are not warranted at this time. The participant successfully administered the dose after reading the IFU (without test administrator prompting).

#### **Subtask 4: Close lips around mouthpiece and breathe in deeply**

There was one reported use error in which the participant held the inhaler in the proper orientation when inhaling during the first two tasks but held the inhaler upside down. No mitigations were proposed. We do not have any recommendation at this time.

### Subtask 6: Close white dust cap

There were three reported close calls reported in which the three participants did not close the white cap prior to inhaling. The participants stated that they expected to use the inhaler as they used their current metered dose inhalers. Another participant stated that they did not fully read the instructions. There were no mitigations proposed; however, labeling changes may help to mitigate this error and we make recommendations in section 4.1.

### **Discrepancies Noted During Review**

We note that the human factors validation report submitted on October 1, 2016 (see Appendix F) differs slightly from the information submitted in response to our June 12, 2017 information request. In the human factors validation report, section 7 'Summary of Formative Evaluations' under 7.2.6 'HF Formative Study 5', Teva utilized two design concepts of the inhaler in which both included an on-product labeling. We note that with regards to labeling, the device used in Formative study 6 was not the same as the device used in the validation study.

Therefore, in our IR we asked for justification and clarification from Teva on the final device design. Teva replied that the inhaler used in the validation study did not contain a label (affixed directly onto the side of the dust cap). This is contradictory to the results shown in the final formative study. The label affixed to the white cap used in the 6<sup>th</sup> formative study provided an additional reminder for patients to close the cap between doses. Therefore, the addition of the affixed label on the white cap may assist in prompting patients to close the cap after a dose. We further note that additional human factors studies are not necessary for the inclusion of the affixed white cap label as the formative study showed that the cap label may be beneficial.

### **3.2 LABELS AND LABELING**

DMEPA also reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We note that changes may be made to the labeling to promote the safe use of the product.

## **4 CONCLUSION & RECOMMENDATIONS**

Overall, our evaluation indicates that during the performance of Task 1, the occurrence of use errors decreased from 1<sup>st</sup> to 2<sup>nd</sup> inhalations. Also, the number of use errors for closing the white cap decreased for the 2<sup>nd</sup> inhalation. Additionally, in Task 2, where the IFU was required, the rate of success amongst participants increased as compared to Task 1 where the IFU was optional. Therefore with repeated use of the inhaler and use of the available labeling, we expect that users will become more familiar with the proper use. However, we recommend changes to the labeling to further help mitigate the risk of users not closing the cap after each inhalation. In addition, since this labeling change was evaluated during the formative study and was found to be helpful, we do not require additional HF data to support this change. We provide our recommendations in Section 4.1.

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

We recommend the following be implemented prior to approval of this NDA:

##### **A. Carton Label and Container Labeling**

1. We note that there were participants in your Human Factors Validation study that did not close the white cap between doses and at the completion of the dose. To attempt to further mitigate this potential error, include the statement 'Close before each inhalation' on both sides of the white cap to further increase the prominence of this step.

##### **B. Instructions for Use and Quick Guide**

1. Update the images of the inhaler to include the above requested labeling change regarding the white cap.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Qvar Redihaler that Teva Pharmaceuticals submitted on October 1, 2016.

| <b>Table 2. Relevant Product Information for Qvar RediHaler</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Initial Approval Date</b>                                    | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Active Ingredient</b>                                        | Beclomethasone Dipropionate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Indication</b>                                               | Maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Route of Administration</b>                                  | Oral Inhalation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Dosage Form</b>                                              | Breath-actuated Inhalation Aerosol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Strength</b>                                                 | 40 mcg and 80 mcg per actuation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Dose and Frequency</b>                                       | 40 mcg to 320 mcg twice daily                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>How Supplied</b>                                             | <b>40 mcg:</b> a box of one 10.6 g canister containing 120 actuations which is enclosed within a sealed beige plastic actuator with a dose counter and hinged white cap, and Patient Information and Instructions for Use; box of one; 120 Actuations<br><b>80 mcg:</b> a box of one 10.6 g canister containing 120 actuations which is enclosed within a sealed maroon plastic actuator with a dose counter and hinged white dust cap, and Patient Information and Instructions for Use; box of one; 120 Actuations |
| <b>Storage</b>                                                  | Store at 25°C (77°F).<br>Excursions between 15° and 30°C (59° and 86°F) are permitted (see USP Controlled Room Temperature)                                                                                                                                                                                                                                                                                                                                                                                          |

**APPENDIX C. HUMAN FACTORS STUDY**

[\\cdsesub1\evsprod\nda207921\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\asthma\5354-other-stud-rep\human-factors-studies\human-factor-study-rpt.pdf](file:///C:/cdsesub1/evsprod/nda207921/0001/m5/53-clin-stud-rep/535-rep-effic-safety-stud/asthma/5354-other-stud-rep/human-factors-studies/human-factor-study-rpt.pdf)

## APPENDIX F. OTHER

### Information Request and Responses:



170614-0017 -  
1.11.4 Response ...

### Email from Medical Officer:



Re NDA 207921 Qvar RediHaler.msg

### Human Factors Report:



Qvar Human  
Factors Study Re...

## **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>c</sup> along with postmarket medication error data, we reviewed the following Qvar RediHaler labels and labeling submitted by Teva Pharmaceuticals on October 1, 2016.

- Container label
- Carton labeling
- Instructions for Use (Image not shown)
- Prescribing Information (Image not shown)

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

#### **Trade Carton**

(b) (4)



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<sup>c</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  
07/11/2017

SARAH K VEE  
07/11/2017

QUYNHNHU T NGUYEN  
07/11/2017

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

**PATIENT LABELING REVIEW**

Date: July 3, 2017

To: Badrul Chowdhury, MD, PhD  
Director  
**Division of Pulmonary, Allergy, and Rheumatology  
Products (DPARP)**

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

Marcia Williams, PhD  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Aman Sarai, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Taylor Burnett, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

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

Drug Name (established name): QVAR Redihaler (beclomethasone dipropionate HFA)

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

Application Type/Number: NDA 207921

Applicant: Teva Branded Pharmaceutical Product R&D, Inc.

## 1 INTRODUCTION

On October 3, 2016, Teva Branded Pharmaceutical Product R&D, Inc. submitted for the Agency's review a New Drug Application for QVAR REDIHALER beclomethasone dipropionate HFA breath-actuated inhalation aerosol. QVAR REDIHALER (beclomethasone dipropionate HFA) is a corticosteroid indicated for the maintenance treatment of asthma as prophylactic therapy in patients 4 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 a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on December 12, 2016 for DMPP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for QVAR REDIHALER (beclomethasone dipropionate HFA) inhalation aerosol, for oral inhalation use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

## 2 MATERIAL REVIEWED

- Draft QVAR REDIHALER (beclomethasone dipropionate HFA) PPI and IFU received on October 3, 2016, and received by DMPP on June 20, 2017.
- Draft QVAR REDIHALER (beclomethasone dipropionate HFA) PPI and IFU received on October 3, 2016, and received by OPDP on June 22, 2017.
- Draft QVAR REDIHALER (beclomethasone dipropionate HFA) Prescribing Information (PI) received on October 3, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on June 20, 2017.
- Draft QVAR REDIHALER (beclomethasone dipropionate HFA) Prescribing Information (PI) received on October 3, 2016, revised by the Review Division throughout the review cycle, and received by OPDP on June 20, 2017.

## 3 REVIEW METHODS

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

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

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI and IFU is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP 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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AMANPREET K SARAI  
07/03/2017

TAYLOR B BURNETT  
07/03/2017

MARCIA B WILLIAMS  
07/03/2017

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

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

## Memorandum

**Date:** July 3, 2017

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

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

**Subject:** NDA 207921  
OPDP labeling comments for QVAR<sup>®</sup> Redihaler<sup>™</sup> (beclomethasone dipropionate HFA) inhalation aerosol, for oral inhalation use (QVAR Redihaler)

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OPDP has reviewed the proposed draft labeling (Package Insert [PI] and Carton and Container Labeling) for QVAR Redihaler submitted for consult on October 24, 2016. OPDP's comments on the proposed Patient Package Insert (PPI) and Instructions for Use (IFU) will be provided at a later date under separate cover in collaboration with the Division of Medical Policy Programs (DMPP).

OPDP's comments on the PI are provided directly in the marked-up document attached (see below) and are based on the proposed draft marked-up labeling available via SharePoint at:

[http://sharepoint.fda.gov/orgs/CDER-ODEII-DPARP/RPM/Laura/NDA\\_207921\\_Consultants\\_Label\\_Review.docx](http://sharepoint.fda.gov/orgs/CDER-ODEII-DPARP/RPM/Laura/NDA_207921_Consultants_Label_Review.docx)

OPDP has no comments on the proposed carton and container labeling at this time.

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

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

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/s/  
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TAYLOR B BURNETT  
07/03/2017

**DEPARTMENT OF HEALTH & HUMAN SERVICES**  
Public Health Service  
Food and Drug Administration  
Center for Devices and Radiological Health  
Office of Compliance, Division of Manufacturing and Quality  
Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch

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**Date:** January 31, 2017  
**To:** Bamidele (Florence) Aisida, CDER/OPQ/OPRO/DRBPMI/RBPMBI, WO75 RM4509, Tel: 240-402-2691; E.M: [Bamidele.Aisida@fda.hhs.gov](mailto:Bamidele.Aisida@fda.hhs.gov)  
Steven Kinsley, CDER/OPQ/OPRO/DRBPMI/RBPMBI, WO75 RM4668, Tel: 240-402-2773, E.M: [Steven.Kinsley@fda.hhs.gov](mailto:Steven.Kinsley@fda.hhs.gov)  
**CC:** Office of combination products at [combination@fda.gov](mailto:combination@fda.gov)  
**Through:** Francisco Vicenty, Branch Chief, CDRH/OC/DMQ/REGO, WO-66, Rm 3426  
**From:** Rakhi Dalal, Ph.D, CDRH/OC/DMQ/REGO, WO-66, Rm 3454  
**Applicant:** Norton (Waterford) Limited  
Unit 301, IDA Industrial Park, Cork Road  
Waterford, Ireland  
FEI: Not Available

**Co- Sponsor:** Teva Branded Pharmaceutical Products R&D Inc.  
41 Moores Road  
Frazer, PA 19355  
FEI: 1000307054

**Application #** NDA 207921, Original NDA submission  
**Product Name:** QVAR Redihaler, Beclomethasone Dipropionate Breath-Actuated Inhalation (BAI) Aerosol (TV-44643), 40 mcg, 80 mcg  
**ICCR (CTS)#** ICC1600718  
**Device Constituent:** Inhaler (Aerosol). This is a breath-actuated inhalation aerosol (or metered dose inhaler)  
**Intended Use:** Maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. (b) (4)  
(b) (4)

**Consult**  
**Instructions:** Review per 820 regulations, NDA 207921 3.2.P

**Pre-Approval**  
**Inspection:** Yes, Inspection Guidance, Page 23.  
**Documentation**  
**Review:** NDA 207921 information – Adequate.  
**CDRH/OC**  
**Recommendation:** Approvable, Page 22.

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**Background:**

The CDER consult request is for a 21 CFR 820 review of the Initial submission NDA 207921, for QVAR Redihaler, Beclomethasone Dipropionate Breath-Actuated Inhalation (BAI) Aerosol (TV-44643), 40

mcg, 80 mcg. Per Cover Letter dated October 1, 2016, Teva Branded Pharmaceutical Products R&D Inc. (Teva) has submitted the NDA on behalf of Norton (Waterford) Limited for beclomethasone dipropionate breath-actuated inhalation (BAI) aerosol (TV-44643) indicated in the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. Beclomethasone dipropionate BAI is also indicated for asthma patients who require systemic corticosteroid administration, where adding beclomethasone dipropionate may reduce or eliminate the need for the systemic corticosteroids. Beclomethasone dipropionate is currently marketed in the US by Teva as QVAR® (beclomethasone dipropionate hydrofluoroalkane [HFA]) Inhalation Aerosol (Teva Respiratory, LLC, Horsham, PA; NDA 020911). QVAR Inhalation Aerosol is indicated in the maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older and for patients with asthma who require systemic corticosteroid treatment, where adding QVAR Inhalation Aerosol may reduce or eliminate the need for systemic corticosteroids. QVAR Inhalation Aerosol delivers beclomethasone dipropionate through a metered-dose inhaler (MDI) and was approved in September 2000. Per the firm, although the MDI is a commonly used device for the delivery of inhaled corticosteroids (ICSs), it requires coordination of actuation and inhalation for effective delivery of the therapeutic agent, as an alternative to the conventional MDI, Teva has developed a breath-actuated inhaler (BAI) MDI, which ensures that actuation of the metered-dose valve occurs automatically when the patient inhales. The proposed tradename is QVAR® REDIHALER™ QVAR REDIHALER contains the same active ingredient as BECLOVENT® Inhalation Aerosol (NDA 018153, GlaxoSmithKline). At the time of this NDA, BECLOVENT is claimed to be discontinued and is no longer marketed. IND 114,865 for BDP BAI was developed for the 505(b)(2) pathway relying on the reference product, QVAR® beclomethasone dipropionate inhalation aerosol (QVAR MDI), approved under NDA 20-911 for the same indications and at the same dosages. IND (b) (4) for the BAI device and the QVAR canister to deliver BDP, for safety and efficacy in adults and adolescents patients was discontinued due to business reasons. The product is approved in the UK in September 2004 as QVAR Easi-Breathe via a national variation to the license for QVAR Inhalation Aerosol and remains available on the UK market. QVAR Easi-Breathe is not marketed in any other country. Per the firm the current NDA BDP BAI has similar BAI design to that used in QVAR Easi-Breathe product, however modified to include 1) an integrated dose counter and 2) a mouthpiece that matches the shape of the standard QVAR MDI actuator. In the US, development of this product has been resumed with an updated BAI device that uses the same BDP formulation as QVAR MDI. Per Section 3.2.P.2, the design and development process followed the streamlined approach for combination products in accordance with CGMPs (21 CFR part 211) and (21 CFR part 820.20, 820.30, 820.50 and 820.100).

The memo contains Facilities/Regulatory History review and documentation in NDA 207921. The CDRH/OC recommendations are provided on Page 22 in the memo.

3.2.P.1 Description and Composition of the Drug Product [beclomethasone dipropionate HFA breath actuated inhalation aerosol, pressurized inhalation solution]

#### 1. DESCRIPTION

Beclomethasone dipropionate HFA breath-actuated inhalation aerosol (BDP BAI) contains a solution of the active drug substance beclomethasone dipropionate (BDP) (b) (4). BDP BAI also contains propellant 1,1,1,2 tetrafluoroethane referred to as HFA-134a. Two strengths have been developed to deliver 40 mcg per actuation and 80 mcg per actuation. Each strength of the product delivers a minimum of 120 actuations.

#### 2. COMPOSITION

BDP BAI 40 mcg, 120 actuation drug product is formulated to deliver 40 mcg per actuation (exactor) or 50 mcg (b) (4) of BDP and at least 120 actuations from each canister. Table 1 outlines the quantities and function of the active ingredient and excipient per container and the quality standards for BDP BAI 40 mcg. The quantity of active ingredient and excipient per actuation (b) (4) is also detailed.

Table 1: Quantity per container and per actuation (b) (4) BDP BAI 40 mcg.

| Ingredient                        | Quantity per container (g) | Quantity per actuation (ex-valve) (mg) | Function          | Reference to standard |
|-----------------------------------|----------------------------|----------------------------------------|-------------------|-----------------------|
| Beclomethasone dipropionate       | (b) (4)                    | (b) (4)                                | Active ingredient | USP                   |
| (b) (4)                           |                            |                                        |                   |                       |
| HFA-134a                          |                            |                                        | Propellant        | In-House              |
| Target fill weight per container. | 10.600                     |                                        |                   |                       |
| (b) (4)                           |                            |                                        |                   |                       |

BDP BAI 80 mcg, 120 actuation drug product is formulated to deliver 80 mcg per actuation exactuator) or 100 mcg (b) (4) of BDP and at least 120 actuations from each canister. The Table 2 outlines the quantities and function of active ingredient and excipient per container and the quality standards for BDP BAI 80 mcg. The quantity of active ingredient and excipient per actuation (ex-valve) is also detailed.

Table 2: Quantity per container and per actuation (b) (4)BDP BAI 80 mcg.

| Ingredient                        | Quantity per container (g) | Quantity per actuation (ex-valve) (mg) | Function          | Reference to standard |
|-----------------------------------|----------------------------|----------------------------------------|-------------------|-----------------------|
| Beclomethasone dipropionate       | (b) (4)                    | (b) (4)                                | Active ingredient | USP                   |
| (b) (4)                           |                            |                                        |                   |                       |
| HFA-134a                          |                            |                                        | Propellant        | In-House              |
| Target fill weight per container. | 10.600                     |                                        |                   |                       |
| (b) (4)                           |                            |                                        |                   |                       |

### 3. CONTAINER CLOSURE

3.5.4.1. Valve Selection and Development: The initial BDP BAI device was designed to operate with the currently marketed QVAR® HFA MDI aerosol canister using a (b) (4) valve, which was submitted in PIND 114865, 28/09/2012. Per FDA’s feedback, Teva performed a Human Factors Engineering testing in collaboration with (b) (4) to assess design usability. Results from the initial Formative Study, the IFU, a Risk Assessment (user Failure Mode and Effects Analysis), and a Protocol for Summative Usability Testing (Summative Protocol) were submitted to the FDA on 30/05/2013 (Sequence 9905) for feedback. Based on the feedback on the priming instruction, Teva changed from a (b) (4) valve (a (b) (4)) to a “primeless” or free flow valve that does not require priming or re-priming throughout the life of the product. In addition to introducing the use of a primeless valve, the manufacture of the canister pack was moved to Teva Pharmaceuticals Ireland (TPI) rather than sourcing from (b) (4). The manufacture of the drug product is described in Section 3.2.P.1 and Section 3.2.P.3.3. The differences in product and manufacturing are summarized on Table 2.

Table 2: Manufacturing and Product Changes

(b) (4)

3.5.4.2. Comparison of a Primeless (b) (4) Valve to a Standard Dose Retention Valve, Figure 9 (side by side comparison of both valves), Figure 10 (Expanded version of Primeless (b) (4) Valve), and Table 3 (comparison of BDP BAI incorporating either a traditional or primeless valve, to a conventional “press and breathe” pMDI with a traditional valve (b) (4)). Unlike the standard MDI, the primeless (b) (4) valve samples a dose immediately before actuation and so avoids the risk outlined above. BDP BAI is designed such that the firing of the canister is controlled mechanically in coordination with the patient’s inhalation

(b) (4)

Table 3: Differences between a Traditional pMDI and Previous BDP BAI and the Redesigned BDP BAI (Current)

|                               | Traditional “Press and breathe” pMDI | Previous BDP BAI with standard dose retention valve | Current BDP BAI with primeless (b) (4) valve |
|-------------------------------|--------------------------------------|-----------------------------------------------------|----------------------------------------------|
| Priming/re-priming            | Required                             | Required                                            | Not required                                 |
| Press and breath coordination | Required                             | Not required                                        | Not required                                 |
| Timing of cap closure         | Not applicable                       | Close cap (b) (4) to ensure correct dosing          | Not applicable                               |
| Orientation when closing cap  | Not applicable                       | Close cap (b) (4) to ensure correct dosing          | Not applicable                               |

**Beclomethasone dipropionate HFA breath-actuated inhalation aerosol (BDP BAI):**

The BDP BAI formulation is contained in a (b) (4) aluminum canister closed with a 50 mL primeless metering valve. The canister is combined with a breath-actuated inhaler (BAI). The

assembled unit consists of the filled canister and a breath actuated inhaler device. The BAI device consists of the three sub-assemblies:

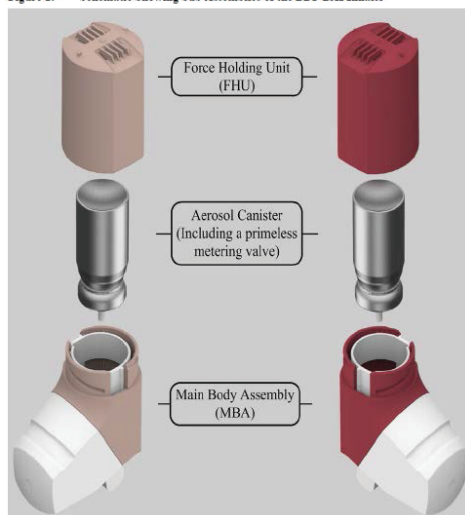
1. A Main Body Assembly (MBA) which includes the actuator and integrated dose counter
2. A filled canister closed by a primeless (b) (4) valve
3. A Force Holding Unit (FHU).



(b) (4)

The component composition for 40 mcg and 80 mcg drug products are identical except for the external colors of the FHU and MBA. A beige FHU and MBA are used for the 40 mcg DP, and a maroon FHU and MBA are used for the 80 mcg DP. A white mouthpiece cover is used for both drug products.

Figure 1: Schematic Showing Sub Assemblies of the BDP BAI Inhaler



Per the firm, the design of the BAI actuator is based on a patented aerosol inhaler device which synchronizes dispensing of a metered dose of BDP with the patient's inhalation through the mouthpiece. Traditional devices require the patient to co-ordinate their inhalation with manual actuation for dispensing the aerosol. The BAI device removes the necessity for the patient to co-ordinate actuation with inhalation, and thereby reduces the possibility of insufficient drug delivery to the lungs caused by lack of co-ordination between inhalation and actuation of the aerosol canister. The selection criteria for the container closure system were as follows: Compatibility with the formulation, robustness to withstand the vapour pressure of the propellant system (b) (4), good dose to dose reproducibility and relatively inert components.

#### Mode/Mechanism of Operation:

##### 2.1. BDP BAI Principle Mode of Operation

The principle mode of operation of the BDP BAI device is described below and involves 3 primary steps OPEN, INHALE, and CLOSE. Figure 1 provides a graphical illustration of the patient usage steps and detail on BDP BAI device operation.

**CDRH/OC Comment:** Information provided is deemed acceptable. Verification of the Production and Process Controls activities under 21 CFR 820.70 is recommended at the TEVA due to the assembly of various components of BDP-BAI for NDA207921.

**Management Responsibility (21 CFR 820.20):**

**Section 5.0 QUALITY SYSTEMS PROCEDURES**

The firm provided a summary of the Quality Policy in the NDA. Per the firm, the responsibilities are fully defined in the TPI's 'Quality Policy'. Briefly, the Site Quality Head has overall responsibility for all Quality matters. The Site Quality Head is the designated responsible person has responsibility for ensuring all Quality Systems are adhered to in their respective areas of responsibility.

The Quality Policy contains an overview of the Quality Management System (QMS), outlining its operation and control. Standard Operating Procedures (SOPs) instruct in its implementation. The QMS is based on and in compliance with the US and EU regulations.

- The Code of Federal Regulations 21 CFR 4, 10.90, 11, 210, 211, 314, 820.20, 820.30, 820.50 and 820.100, (820.170 and 820.200 for reference only) ;
- Directive 2001/83/EC – Medicinal Products for Human Use
- As well as Teva Corporate Policies

Per the firm, the assurance of quality, consistency, safety and efficacy of products is fundamental to all work undertaken by Teva Pharmaceuticals Ireland and is practiced by all personnel in their day-to-day activities through the implementation of current Good Manufacturing Practices (cGMP). It is the responsibility of both the Quality Assurance/Compliance functions to monitor the Quality System through regular audit, by change control and by annual product reviews, in order to verify the ongoing application of the system and the relevant procedures.

**CDRH/OC Comment:** Information provided is deemed acceptable.

**Purchasing Controls (21 CFR 820.50)**

Per the summary provided, all vendors are managed as per the 'Vendor Management Policy'. This system governs the assessment, approval and ongoing management of vendors. This policy outlines the prerequisites required prior to the approval of a Vendor for Development phase, Clinical Trial phase and Commercial use, to assure that a vendor will consistently produce materials, provide equipment or perform a service within the established parameters for quality, purity, integrity and safety. Once approved all vendors are subjected to regular review to appraise the quality, effectiveness and applicability of the material/Vendor. This activity encompasses routine audits, site visits (where applicable) and investigation of any deviations through the sites Deviation Management System (b) (4) with appropriate actions. All approved vendors are added to the site's Approved Vendor List. Each material is purchased against a unique code which has an associated specification to which the supplier has approved and agreed to produce the material too. The material can only be receipted into the organization (i.e. Teva) once the code is approved on the company ERP system through the above process. All receipted materials undergo sampling and inspection and testing for their intended use. Introduction of a new vendor or material and any

vendor related changes are managed through the companies Change Control system (i.e.

(b) (4)

**CDRH/OC Comment:** Information provided is deemed acceptable. Verification of the Purchasing Controls activities under 21 CFR 820.50 is recommended at the time of facility inspection for NDA207921.

**Corrective and Preventive Action (21 CFR 820.100)**

Per the summary provided, Corrective and Preventative Actions (CAPA) is managed via 'Processing of Global Corrective and Preventative Actions (gCAPA) and Associated Records' and 'Management of Corrective and Preventative Actions (CAPA)'. Management of Corrective and Preventative Actions (CAPA) and CAPA effectiveness checks on (b) (4). This system is used to monitor observations from internal audits, external audits or other body audits, incident reports, investigations, deviations, customer complaints, internal reports or any other quality system. (b) (4)

(b) (4) This helps provide relevant information for management review in order to deal effectively with product and quality problems, and to prevent their recurrence.

According to the firm, (b) (4) will all Teva manufacturing sites connected to the same network. Should a CAPA be assessed as impacting Teva multiple sites, CAPAs can be raised for each site from the common incident. In the case of a third party manufacturer or Vendor commits to a CAPA as part of an investigation process, a corresponding CAPA is opened in the Teva (b) (4)

**CDRH/OC Comment:** Information provided is deemed acceptable. It appears from the clinical study outcomes that there were several AEs that required investigation and root cause analysis. This suggests that the applicant TEVA has a CAPA system that is active. Verification of the Corrective and Preventative Actions (CAPA) activities under 21 CFR 820.100 is recommended at the time of facility inspection for NDA207921.

**Deficiencies to be communicated to the sponsor/NDA Holder:**

None

**CDRH Office of Compliance Recommendation**

1. QVAR Redihaler, Beclomethasone Dipropionate Breath-Actuated Inhalation (BAI) Aerosol (TV-44643), 40 mcg, 80 mcg, NDA 207921 information –Adequate.
2. NDA 207921 Approvable
3. Pre-approval inspection recommended. Inspection guidance, Page 23.

Rakhi M. Panguluri - S  
Digitally signed by Rakhi M. Panguluri - S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300200210, cn=Rakhi M. Panguluri - S  
Date: 2017.01.30 18:00:40 -05'00'

Rakhi Dalal, Ph.D.

### **Inspectional Guidance**

CDRH recommends the inspection under the applicable Medical Device Regulations of:

1. Norton (Waterford) Limited  
Unit 301, IDA Industrial Park, Cork Road  
Waterford, Ireland  
**FEI: Not available**

Responsibility: NDA 207921 Holder

Guidance: A comprehensive inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), Final Acceptance Activities (21 CFR 820.80) and CAPA (21 CFR 820.100).

2. Teva Branded Pharmaceutical Products R&D Inc.  
41 Moores Road  
Frazer, PA 19355  
FEI: 1000307054

Responsibility: i) Co-Sponsor of NDA 207921, Cover Letter, 10/01/2016 (US contact for Norton (Waterford) Limited; ii) Drug – device assembly. Per Section 3.2.P.2., [REDACTED] (b) (4)

Guidance: A comprehensive medical device inspection recommended focusing on Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), Production and Process Controls (21 CFR 820.70), Final Acceptance Activities (21 CFR 820.80) and CAPA (21 CFR 820.100).

### **REGULATORY STRATEGY**

The establishment inspection report (EIR) for the firm should be shared with CDRH (through CDER to CDRH as a consult review) if the inspection is being classified Official Action Indicated (OAI). The District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related. Questions regarding this consult should be referred to one of the following individuals:

#### **Primary Contact**

Rakhi Dalal, Ph.D., CSO  
REGO, DMQ, Office of Compliance, WO66 RM 3454  
Phone: 301-796-6116

#### **Secondary Contacts (if Primary is unavailable and a timely answer is required)**

Francisco Vicenty, Branch Chief,  
REGO, DMQ, Office of Compliance, WO66 RM 3426  
Phone: 301-796- 5577

**THIS INSPECTION GUIDANCE IS FOR INTERNAL FDA USE, AND SHOULD NOT BE PROVIDED OR SHOWN TO THE FIRM DURING INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION.**

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/s/  
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BAMIDELE F AISIDA  
01/31/2017

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

| Application Information                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NDA # 207921<br>BLA#                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | NDA Supplement #: S-<br>BLA Supplement #: S- | Efficacy Supplement Category:<br><input type="checkbox"/> New Indication (SE1)<br><input type="checkbox"/> New Dosing Regimen (SE2)<br><input type="checkbox"/> New Route Of Administration (SE3)<br><input type="checkbox"/> Comparative Efficacy Claim (SE4)<br><input type="checkbox"/> New Patient Population (SE5)<br><input type="checkbox"/> Rx To OTC Switch (SE6)<br><input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7)<br><input type="checkbox"/> Labeling Change With Clinical Data (SE8)<br><input type="checkbox"/> Manufacturing Change With Clinical Data (SE9)<br><input type="checkbox"/> Animal Rule Confirmatory Study (SE10) |
| Proprietary Name: QVAR® REDIHALER™                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Established/Proper Name: beclomethasone dipropionate<br>Dosage Form: Inhalation Aerosol<br>Strengths: 80, 160, 320, or 640 mcg/day                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Applicant: Norton (Waterford) Ltd.<br>Agent for Applicant (if applicable): Teva Branded Pharmaceutical Products R&D Inc.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Date of Application: October 3, 2016<br>Date of Receipt: October 3, 2016<br>Date clock started after Unacceptable for Filing (UN):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| PDUFA/BsUFA Goal Date: August 3, 2017                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                              | Action Goal Date (if different): August 3, 2017                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Filing Date: December 3, 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                              | Date of Filing Meeting: November 18, 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Chemical Classification (original NDAs only) :<br><input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination<br><input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination<br><input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination<br><input type="checkbox"/> Type 4- New Combination<br><input checked="" type="checkbox"/> Type 5- New Formulation or New Manufacturer<br><input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA<br><input type="checkbox"/> Type 8- Partial Rx to OTC Switch<br><input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval)<br><input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval) |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Proposed indication(s)/Proposed change(s): Maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. <span style="float: right;">(b) (4)</span><br><div style="background-color: #cccccc; width: 100%; height: 15px; margin-top: 5px;"></div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Type of Original NDA:<br>AND (if applicable)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                              | <input type="checkbox"/> 505(b)(1)<br><input checked="" type="checkbox"/> 505(b)(2)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Type of NDA Supplement:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                              | <input type="checkbox"/> 505(b)(1)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

***If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment”  
review found at:***  
<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499>.

505(b)(2)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| Type of BLA                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/> 351(a)<br><input type="checkbox"/> 351(k)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Review Classification:                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <input checked="" type="checkbox"/> Standard<br><input type="checkbox"/> Priority                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>The application will be a priority review if:</b>                                                                                                                                                                                                                                                                                                                                                                                                                     | <input type="checkbox"/> Pediatric WR<br><input type="checkbox"/> QIDP<br><input type="checkbox"/> Tropical Disease Priority Review Voucher<br><input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <ul style="list-style-type: none"> <li>• A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</li> <li>• The product is a Qualified Infectious Disease Product (QIDP)</li> <li>• A Tropical Disease Priority Review Voucher was submitted</li> <li>• A Pediatric Rare Disease Priority Review Voucher was submitted</li> </ul> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Resubmission after withdrawal? <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                  | Resubmission after refuse to file? <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Part 3 Combination Product? <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                     | <input type="checkbox"/> Convenience kit/Co-package<br><input 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) |
| <b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b>                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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| <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 (FDCA Section 505B)<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) |
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Collaborative Review Division (if OTC product):

List referenced IND Number(s):

| Goal Dates/Product Names/Classification Properties                                                                                      | YES                                 | NO                       | NA | Comment |
|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|----|---------|
| PDUFA/BsUFA and Action Goal dates correct in the electronic archive?                                                                    | <input checked="" type="checkbox"/> | <input type="checkbox"/> |    |         |
| <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>       |                                     |                          |    |         |
| Are the established/proper and applicant names correct in electronic archive?                                                           | <input checked="" type="checkbox"/> | <input type="checkbox"/> |    |         |
| <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i> |                                     |                          |    |         |

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| <i>to the supporting IND(s) if not already entered into electronic archive.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                        |                                     |                          |                |
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i><br><a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a><br><i>If no, ask the document room staff to make the appropriate entries.</i> | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                    | <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:</i><br><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a><br><b>If yes, explain in comment column.</b>                                                                                                                                                                                                                                            | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                               | <input checked="" type="checkbox"/> |                          |                |
| <b>If affected by AIP, has OC 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)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                    | <input type="checkbox"/>            |                          |                |
| <u>User Fee Status</u><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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>                                                                                                                                                                                                                                                                                           | Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ):<br><input checked="" type="checkbox"/> Paid<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. Contact the User Fee Staff. If appropriate, send UN letter.</i>                                                                                                                                                                                                                                                                                                    | Payment of other user fees:<br><input checked="" type="checkbox"/> Not in arrears<br><input type="checkbox"/> In arrears                                                                                                                                                                                                                               |                                     |                          |                |
| <u>User Fee Bundling Policy</u><br><i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i><br><a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>                                                                                                                                                                           | Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i><br><input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No                                                                                                                                                  |                                     |                          |                |
| <b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>YES</b>                                                                                                                                                                                                                                                                                                                                             | <b>NO</b>                           | <b>NA</b>                | <b>Comment</b> |
| Is the application a 505(b)(2) NDA? ( <i>Check the 356h form,</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                    | <input type="checkbox"/>            |                          |                |

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| cover letter, and annotated labeling). <b>If yes</b> , answer the bulleted questions below:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                     |                                     |                                     |                |  |
| • Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                     | <input type="checkbox"/>            | <input checked="" 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"/>            | <input checked="" 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"/>            | <input checked="" type="checkbox"/> |                |  |
| <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>                                                                                                                                                                                                                                                                                                                                                                   |                                     |                                     |                                     |                |  |
| • Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                     | <input type="checkbox"/>            | <input checked="" 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</b> , please list below:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                     |                                     |                                     |                |  |
| Application No.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Drug Name                           | Exclusivity Code                    | Exclusivity Expiration              |                |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                     |                                     |                                     |                |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                     |                                     |                                     |                |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                     |                                     |                                     |                |  |
| <i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i> |                                     |                                     |                                     |                |  |
| <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 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>                                                                                                                                                                                                                                                                                   | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                                     |                |  |
| <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)(14)]?                                                                                                                                                                                                                                                                                                                                                                                                             | <input type="checkbox"/>            | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                |  |
| <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                     |                                     |                                     |                |  |
| <b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <input checked="" type="checkbox"/> | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                |  |
| <b>If yes</b> , # years requested: 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                     |                                     |                                     |                |  |
| <i>Note: An applicant can receive exclusivity without requesting it;</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                     |                                     |                                     |                |  |

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| <i>therefore, requesting exclusivity is not required.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                          |                                     |                                     |  |
| <b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <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"/>            | <input checked="" type="checkbox"/> |  |
| <b>BLAs only:</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, CDER Purple Book Manager</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 checked="" type="checkbox"/> |  |

| Format and Content                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                   |                          |                          |                |
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| <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><input checked="" type="checkbox"/> All electronic<br><input type="checkbox"/> Mixed (paper/electronic)<br><br><input checked="" type="checkbox"/> 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).                                                                              | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                               | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <b>Index:</b> Does the submission contain an accurate comprehensive index?                                                                                                                                     | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                               | <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><input checked="" type="checkbox"/> legible | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                               | <input type="checkbox"/> |                          |                |

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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                     |                          |                                     |                |
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| <input checked="" type="checkbox"/> English (or translated into English)<br><input checked="" type="checkbox"/> pagination<br><input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)                                                                                                                                                                                                                                                                                                                                 |                                     |                          |                                     |                |
| <b>If no, explain.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                     |                          |                                     |                |
| <b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                |
| <b>If yes, BLA #</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                     |                          |                                     |                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                     |                          |                                     |                |
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| <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 (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i> |                                     |                          |                                     |                |
| <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)?                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                                     |                |
| <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                     |                          |                                     |                |
| Are all establishments and their registration numbers listed on the form/attached to the form?                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            |                |
| <b>Patent Information (NDAs/NDA efficacy supplements only)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <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)?                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <input checked="" type="checkbox"/> | <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 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?                                                                                                                                                                                                                                                                                                                                                                                                                                | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                                     |                |
| <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                     |                          |                                     |                |
| <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                     |                          |                                     |                |
| <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?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                                     |                |
| <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                     |                          |                                     |                |
| <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>                                                                                                                                                                                                                                                                                                                                                                                                                 |                                     |                          |                                     |                |

| <b>Debarment Certification</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <b>YES</b>                          | <b>NO</b>                           | <b>NA</b>                           | <b>Comment</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-----------------------------------------------------------------------------------------------------|
| <p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><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></p> <p><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></p> | <input checked="" type="checkbox"/> | <input type="checkbox"/>            | <input type="checkbox"/>            |                                                                                                     |
| <b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <b>YES</b>                          | <b>NO</b>                           | <b>NA</b>                           | <b>Comment</b>                                                                                      |
| <p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><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></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>                                                                                                                                                                                                                                                                                                           | <input type="checkbox"/>            | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                                                                                                     |
| <b>Controlled Substance/Product with Abuse Potential</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <b>YES</b>                          | <b>NO</b>                           | <b>NA</b>                           | <b>Comment</b>                                                                                      |
| <p><u>For NMEs:</u><br/>Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u><br/><i>Date of consult sent to Controlled Substance Staff :</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <input type="checkbox"/>            | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                                                                                                     |
| <b>Pediatrics</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <b>YES</b>                          | <b>NO</b>                           | <b>NA</b>                           | <b>Comment</b>                                                                                      |
| <p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                                     | <p>beclomethasone dipropionate BAI is neither a new active ingredient, indication, dosage form,</p> |

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

Version: 9/29/2016

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|                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                     |                                     |                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------------------|
| <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                     |                                     | dosing regimen, or new route of administration   |
| <b>If the application triggers PREA</b> , is there an agreed Initial Pediatric Study Plan (iPSP)?<br><br><i>If no, may be an RTF issue - contact DPMH for advice.</i>                                                                                                                                                                                                            | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/>            | <input type="checkbox"/>            | iPSP submitted under IND 114865 on July 18, 2014 |
| <b>If required by the agreed iPSP</b> , are the pediatric studies outlined in the agreed iPSP completed and included in the application?<br><br><i>If no, may be an RTF issue - contact DPMH for advice.</i>                                                                                                                                                                     | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/>            | <input type="checkbox"/>            |                                                  |
| <b>BPCA:</b><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"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <input checked="" type="checkbox"/> |                                     |                                                  |
| <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>                                                                                                                                                                                          | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/>            | <input type="checkbox"/>            |                                                  |
| <b>REMS</b>                                                                                                                                                                                                                                                                                                                                                                      | <b>YES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <b>NO</b>                           | <b>NA</b>                           | <b>Comment</b>                                   |
| 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"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <input type="checkbox"/>            | <input checked="" 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 (Prescribing Information)(PI)<br><input checked="" type="checkbox"/> Patient Package Insert (PPI)<br><input checked="" type="checkbox"/> Instructions for Use (IFU)<br><input checked="" type="checkbox"/> Medication Guide (MedGuide)<br><input checked="" type="checkbox"/> Carton labeling<br><input checked="" type="checkbox"/> Immediate container labels<br><input type="checkbox"/> Diluent labeling<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>                                                                                                                                                                                                                                    | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/>            |                                     |                                                  |
| Is the PI submitted in Physician Labeling Rule (PLR)                                                                                                                                                                                                                                                                                                                             | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/>            |                                     |                                                  |

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

|                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                  |                                                          |                                                          |                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|----------------|
| format? <sup>4</sup>                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                  |                                                          |                                                          |                |
| <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"/>                                 | <input checked="" type="checkbox"/>                      |                |
| <b>For applications submitted on or after June 30, 2015:</b><br>Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?<br><br>Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?                                                                                                                             | <input checked="" type="checkbox"/><br><br><input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/><br><br><input type="checkbox"/> | <input type="checkbox"/><br><br><input type="checkbox"/> |                |
| <b>For applications submitted on or after June 30, 2015:</b><br><b>If PI not submitted in PLLR 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 PLLR format before the filing date.</i> | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/>                                 | <input checked="" type="checkbox"/>                      |                |
| Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?                                                                                                                                                                                                                                                                                        | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/>                                 | <input type="checkbox"/>                                 |                |
| Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? ( <i>send WORD version if available</i> )                                                                                                                                                                                                                                                                                                | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/>                                 | <input type="checkbox"/>                                 |                |
| Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?                                                                                                                                                                                                                  | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/>                                 | <input type="checkbox"/>                                 |                |
| <b>OTC Labeling</b>                                                                                                                                                                                                                                                                                                                                                                                                    | <input checked="" type="checkbox"/> <b>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/ImmediateOffice/LabelingDevelopmentTeam/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 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)                  | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <i>If yes, specify consult(s) and date(s) sent:</i><br>PLT/December 9, 2016, OSE/October 24, 2016, DDMAC/October 24, 2016 |                                     |                          |                          |                |
| <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 23, 2014                                                            | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                          |                |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?<br><b>Date(s):</b> May 15, 2015                                                | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                          |                |
| Any Special Protocol Assessments (SPAs)?<br><b>Date(s):</b>                                                               | <input type="checkbox"/>            |                          |                          |                |

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** December 7, 2016

**BACKGROUND:** Teva's submitted a 505(b)2 application for beclomethasone dipropionate, QVAR® Redihaler. The sponsor developed a breath-actuated inhaler (BAI), which ensures the actuation of a metered-dose valve that occurs automatically when patients inhale. Teva is referencing BECLOVENT® Inhalation Aerosol (NDA 018153, GlaxoSmithKline), which is no longer marketed. Beclomethasone dipropionate, is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older and [REDACTED] (b) (4)

**REVIEW TEAM:**

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

|                       |           |               |   |
|-----------------------|-----------|---------------|---|
|                       | TL:       |               |   |
| Clinical Pharmacology | Reviewer: | Johnny Lau    | Y |
|                       | TL:       | Anshu Marathe | Y |
| • Genomics            | Reviewer: |               |   |
| • Pharmacometrics     | Reviewer: |               |   |
| Biostatistics         | Reviewer: | Mingyu Xi     | Y |
|                       | TL:       | Gregory Levin | N |

|                                                                            |           |                     |   |
|----------------------------------------------------------------------------|-----------|---------------------|---|
| Nonclinical<br>(Pharmacology/Toxicology)                                   | Reviewer: | Xiaochun Chen       | Y |
|                                                                            | TL:       | Carol Galvis        | Y |
| Statistics (carcinogenicity)                                               | Reviewer: |                     |   |
|                                                                            | TL:       |                     |   |
| Product Quality (CMC) Review Team:                                         | ATL:      | Craig Bertha        | Y |
|                                                                            | RBPM:     | Bamidele Aisida     | N |
| • Drug Substance                                                           | Reviewer: | Debasis Ghosh       | N |
| • Drug Product                                                             | Reviewer: | Venkat Pavaluri     | Y |
| • Process                                                                  | Reviewer: | Brian Rogers        | N |
| • Microbiology                                                             | Reviewer: | Daniel Schu         | N |
| • Facility                                                                 | Reviewer: | Aditi Thakur        | N |
| • Biopharmaceutics                                                         | Reviewer: |                     |   |
| • Immunogenicity                                                           | Reviewer: |                     |   |
| • Labeling (BLAs only)                                                     | Reviewer: |                     |   |
| • Other (e.g., Branch Chiefs, EA Reviewer)                                 |           |                     |   |
| OMP/OMPI/DMPP (MedGuide, PPI, IFU)                                         | Reviewer: |                     |   |
|                                                                            | TL:       |                     |   |
| OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling) | Reviewer: | Taylor Burnett      | N |
|                                                                            | TL:       | Kathleen Klemm      | N |
| OSE/DMEPA (proprietary name, carton/container labeling)                    | Reviewer: | Lissa Pringle-Owens | N |
|                                                                            | TL:       | Mishale Mistry      | N |
| OSE/DRISK (REMS)                                                           | Reviewer: |                     |   |
|                                                                            | TL:       |                     |   |
| OC/OSI/DSC/PMSB (REMS)                                                     | Reviewer: |                     |   |
|                                                                            | TL:       |                     |   |

|                                                                                                                                                                                |           |                                                                        |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|------------------------------------------------------------------------|--|
| Bioresearch Monitoring (OSI)                                                                                                                                                   | Reviewer: |                                                                        |  |
|                                                                                                                                                                                | TL:       |                                                                        |  |
| Controlled Substance Staff (CSS)                                                                                                                                               | Reviewer: |                                                                        |  |
|                                                                                                                                                                                | TL:       |                                                                        |  |
| Other reviewers/disciplines                                                                                                                                                    |           |                                                                        |  |
| <ul style="list-style-type: none"> <li><b>Discipline</b></li> </ul> <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p> | Reviewer: |                                                                        |  |
|                                                                                                                                                                                | TL:       |                                                                        |  |
| Other attendees                                                                                                                                                                |           |                                                                        |  |
|                                                                                                                                                                                |           |                                                                        |  |
|                                                                                                                                                                                |           |                                                                        |  |
|                                                                                                                                                                                |           |                                                                        |  |
|                                                                                                                                                                                |           | *For additional lines, right click here and select "insert rows below" |  |

**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., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</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>The sponsor relies on the previously approved product ( QVAR Inhalation Aerosol, QNASL™ Nasal Aerosol, and BECLOVENT and reliance on FDA's previous finding of safety and efficacy. |
| <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<br><input checked="" type="checkbox"/> No comments                                                                                                                                                                                                                                                                                           |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <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 checked="" type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?<br/> <b>If no</b>, explain: The sponsor conducted 4 Phase 3 clinical studies (BDB-AS-301, BDB-AS-302, BDB-AS-304, and BDB-AS-30039).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                  | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO                                                                                                                                    |
| <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>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>CONTROLLED SUBSTANCE STAFF</b></p> <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            |
| <p><b>CLINICAL MICROBIOLOGY</b></p> <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            |

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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <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 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 |
| <p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</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>PRODUCT QUALITY (CMC)</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><u>New Molecular Entity (NDAs only)</u></b></p> <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>                                                                                                               | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO                                                                                                                         |
| <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>Comments:</b></p> | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO<br><br><input type="checkbox"/> YES<br><input type="checkbox"/> NO                                                      |
| <p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <p><b>Comments:</b></p>                                                                                    | <input type="checkbox"/> Not Applicable<br><br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO                                                                          |

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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>                                                                                                                                                                                                                                                                                                                                                                          | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input type="checkbox"/> Review issues for 74-day letter |
| <p><b><u>CMC Labeling Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>                                                                                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/> Review issues for 74-day letter                                                                                                                                   |
| <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> | <input checked="" type="checkbox"/> N/A<br><br><input type="checkbox"/> YES<br><input type="checkbox"/> NO<br><br><input type="checkbox"/> YES<br><input type="checkbox"/> NO              |
| <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>                                                                                                                                                                                                                                                  | <input type="checkbox"/> YES<br><input type="checkbox"/> NO                                                                                                                                |
| <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>                                                                                                                                                                                                                                                                                               | <input type="checkbox"/> YES<br><input type="checkbox"/> NO                                                                                                                                |
| <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>                                                                                                                                                                                                                                                                                     | <input type="checkbox"/> YES<br><input type="checkbox"/> NO                                                                                                                                |

| <b>REGULATORY PROJECT MANAGEMENT</b>                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Signatory Authority:</b> Badrul Chowdhury, M.D.                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V):<br>February 28, 2017                       |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional): |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Comments:</b>                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <input type="checkbox"/>                                                                                                  | The application is unsuitable for filing. Explain why:                                                                                                                                                                                                                                                                                                                                                                                  |
| <input checked="" type="checkbox"/>                                                                                       | The application, on its face, appears to be suitable for filing.<br><br><u>Review Issues:</u><br><br><input type="checkbox"/> No review issues have been identified for the 74-day letter.<br><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.<br><br><u>Review Classification:</u><br><br><input checked="" type="checkbox"/> Standard Review<br><input type="checkbox"/> Priority Review |
| <b>ACTION ITEMS</b>                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/>                                                                                       | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).                                                                                                                                                                                                                        |
| <input type="checkbox"/>                                                                                                  | If RTF, notify everyone who already received a consult request, OSE PM, and RBPM                                                                                                                                                                                                                                                                                                                                                        |
| <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"/>                                                                                                  | If priority review, notify applicant in writing by day 60 (see CST for choices)                                                                                                                                                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/>                                                                                       | Send review issues/no review issues by day 74                                                                                                                                                                                                                                                                                                                                                                                           |
| <input checked="" type="checkbox"/>                                                                                       | 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 applications in the Program)                                                                                                                                                                                                                                                                                                                                                                        |
| <input type="checkbox"/>                                                                                                  | Other                                                                                                                                                                                                                                                                                                                                                                                                                                   |

Annual review of template by OND ADRAAs completed: April 2016

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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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LAURA MUSSE  
12/13/2016