CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207921Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207921 SUPPL # HFD #

Trade Name QVAR® REDIHALER™

Generic Name beclomethasone dipropionate

Applicant Name Norton (Waterford) Ltd.

Approval Date, If Known August 3, 2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the

NDA #(s).

NDA# 020911	QVAR (beclomethasone dipropionate) Inhalation Aerosol
NDA# 018153	BECLOVENT, (beclomethasone dipropionate) Inhalation Aerosol
NDA# 202813	QNASL (beclomethasone dipropionate) Inhalation Aerosol

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability

studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could

independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

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).

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

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).

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 114865 YES ☒ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Laura Musse
Title: Regulatory Health Project Manager
Date: August 3, 2017

Name of Division Director signing form: Badrul Chowdhury, M.D.

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

LAURA MUSSE
08/03/2017

BADRUL A CHOWDHURY
08/03/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 207921	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: QVAR® REDIHALER™ Established/Proper Name: beclomethasone dipropionate Dosage Form: Inhalation Aerosol		Applicant: Norton (Waterford) Ltd. Agent for Applicant : Teva Branded Pharmaceutical Products R&D Inc.
RPM: Laura Musse, RN, MS, CRNP		Division: Division of Pulmonary, Allergy, and Rheumatology Product

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: July 10, 2017

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is October 3, 2018	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) August 3, 2017
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☒ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Acceptability: December 19, 2016 Review: December 16, 2016
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ July 23, 2017 DMEPA: ☒ July 11, 2017 DMPP/PLT (DRISK): ☒ July 3, 2017 OPDP: ☒ July 3, 2017 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ Human Factors Report July 11, 2017
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	December 13, 2016 August 2, 2017 ☐ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed August 3, 2017
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: beclomethasone dipropionate HFA Breath-Actuated Inhalation Aerosol was exempt from the PREA requirements on September 30, 2014 because it was not a new active ingredient, indication, dosage form, dosing regimen or route of administration and the Applicant confirmed there have been no changes to the development program.	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	July 5, 2017, June 22, and June 6, 15 and 22, 2017 and, May 30, 2017, March 10, 2017, February 21, 2017 January 17, 2017, December 12, 2016, November 20, 2016, October 21, 2016
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ April 28, 2015
• EOP2 meeting *(indicate date of mtg)*	☒ October 6, 2014
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None
Division Director Summary Review *(indicate date for each review)*	☐ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
• Clinical review(s) *(indicate date for each review)*	November 23, 2016, June 29, 2017
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Primary Review, page 6/Section 41
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☒ June 23, 2017, December 1, 2016

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ December 2, 2016
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ July 6, 2017
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ July 6, 2017, June 29, 2017, November 23, 2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	June 28, March 29, 2017, October17, 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ May 15, 2017, January 31, 2017
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	June 28, 2017
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☒ N/A *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☒ N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ N/A
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ N/A
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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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.

/s/

LAURA MUSSE
08/03/2017

From: Musse, Laura
Sent: Friday, July 07, 2017 2:14 PM
To: Arthur Merlin Destreux
Subject: NDA 207921 Official Labeling IR forthcoming

I am waiting for clearance on the 4th labeling IR. This IR contains minor edits to the PI submitted from one of the reviewers. I have attached it so that you can have a head-start if you are currently working on the labeling revisions.

Thanks, Laura Musse

[redacted]

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/s/

LAURA MUSSE
08/01/2017

NDA 207921
beclomethasone dipropionate
Teva

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: July 5, 2017

To: Arthur Merlin Destreux, M.S. Associate Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 610-786-7051	**Fax number:** (301) 796-9728
Phone number: 610-727-6125	**Phone number:** (240) 402-3720

Subject: NDA 207921 (beclomethasone dipropionate) Information Request for labeling

Total no. of pages including cover: 30

Comments: Please confirm receipt at laura.musse@fda.hhs.gov

Document to be emailed to: Arthur.MerlinDestreux@tevapharm.com (Secured email)

NDA 207921
beclomethasone dipropionate
Teva

Your submission, dated October 3, 2016 to NDA 207921, is currently under review. We have the following comments and requests for information:

We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, and deletions are in strike-out. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Submit revised labeling incorporating the changes shown in the attached marked-up label and a tracked change version of the label incorporating our recommended changes via email (Laura.Musse@fda.hhs.gov) by COB on Monday, July 10, 2017. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact me at Laura Musse, at 240-402-3720.

Review/History Clearance

Drafted by: L. Musse: Date: July 5, 2017
Clearance: S. Barnes: Date: July 5, 2017
Finalized: L. Musse: Date: July 5, 2017
File Name: Label 3rd Round: Date: July 5, 2017

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

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/s/

LAURA MUSSE
07/05/2017

NDA 207921
beclomethasone dipropionate
Teva

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: June 22, 2017

To: Arthur Merlin Destreux, M.S. Associate Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company Teva Branded Pharmaceutical Products R&D Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 610-786-7051	**Fax number:** (301) 796-9728
Phone number: 610-727-6125	**Phone number:** (240) 402-3720

Subject: NDA 207921 (beclomethasone dipropionate) Information Request for labeling

Total no. of pages including cover: 22

Comments: Please confirm receipt at laura.musse@fda.hhs.gov

Document to be emailed to: Arthur.MerlinDestreux@tevapharm.com (Secured email)

NDA 207921
beclomethasone dipropionate
Teva

Your submission, dated October 3, 2016 to NDA 207921, is currently under review. We have the following comments and requests for information:

We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, and deletions are in strike-out. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue our review of the label.

Submit revised labeling incorporating the changes shown in the attached marked-up label and a tracked change version of the label incorporating our recommended changes via email (Laura.Musse@fda.hhs.gov) by COB on Wednesday, June 28, 2017. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact me at Laura Musse, at 240-402-3720.

Review/History Clearance

Drafted by: L. Musse: Date: June 21, 2017
Clearance: S. Barnes: Date: June 21, 2017
Finalized: L. Musse: Date: June 21, 2017
File Name: Label 2nd Round: Date: June 21, 2017

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

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/s/

LAURA MUSSE
06/22/2017

From: Aisida, Bamidele (Florence)
To: "Arthur Merlin Destreux"
Cc: Musse, Laura
Subject: NDA 207921 IR 6-15-17
Date: Thursday, June 15, 2017 10:12:31 AM

Dear Arthur,

Please respond to the following with a submission to your NDA by Wednesday, June 21, 2016.

Available stability data from the Exhibit 2 stability program on BDP BAI indicates that there are still some OOT results for Delivered Dose Uniformity (DDU) and also some Out of Trend (OOT) grouping results for Aerodynamic Particle Size Distribution (APSD) at accelerated storage conditions. Based on these observations and the limited stability performance data available on the primeless valve (b) (4) together with the Breath Actuated Inhaler device used during Exhibit 2 stability program we request the following :

1. Revise the post-approval stability protocol and stability commitment as follows: Include accelerated, intermediate and long-term storage conditions, per ICH Q1A (R2) for samples placed in both valve up and inverted (valve down) orientations, with no protective packaging for the first three commercial batches. Submit the amended Post-Approval Stability Protocol and Stability Commitment..
2. Revise the sample collection procedures to include tests that require actuation of the inhaler during the testing, i.e. valve delivery (shot weight), DDU and APSD etc., and include instructions to the operator /analyst to record the external appearance of the canister, particularly if any drug deposition around the base of the valve (b) (4) is observed on individual canisters.

Please confirm receipt of this email.

Thanks,

-Florence

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA. T: 240.402.2691

NDA 207921
QVAR Redihaler (beclomethasone dipropionate inhalation aerosol)
Norton Waterford Limited

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: June 12, 2017

To: Arthur Merlin Destreux, M.S. Associate Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Norton Waterford Ltd c/o Teva Branded Pharmaceutical Products R&D Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 610-786-7051	**Fax number:** (301) 796-9728
Phone number: 610-727-6125	**Phone number:** (240) 402-3720

Subject: NDA 207921 (beclomethasone dipropionate); Information Request

Total no. of pages including cover: 3

Comments: Please confirm receipt at laura.musse@fda.hhs.gov

Document to be emailed to: Arthur.MerlinDestreux@tevapharm.com (Secured email)

Your submission dated October 1, 2016, to NDA 207921, is currently under review. We have the following comments and requests for information pertaining to your Human Factors Study Report:

You have defined the tasks at a high level and we need to review human factors data that are described at the subtask level. In addition, your analyses of the study data appear to be aggregated analysis across all four tasks. Submit a detailed description of all errors, close calls, and instances of test administrator assistance observed in each of the four tasks and associated subtasks. Specifically, for task and associated subtask, include number and description of failures/use errors, close calls, use difficulties, subjective data from study participants, root cause analysis, and mitigation strategies. If further mitigations are not proposed for an error, include your justification. Submit this in a tabular format (see example below), if possible, to facilitate our review for each of the four high level tasks. Note that instances where test administrator provided assistance should be considered as a task failure/use error.

Task 1: IFU Use Optional					
	Number of Failure/Use Errors, Close Call, Use Difficulties	**Description of Use Errors, Close Call, Use Difficulties**	**Subjective Data from Study Participants for each failure/use error, close call, use difficulty**	**Root Cause Analysis**	**Mitigation strategies and/or Justification**
Subtask 1: xxxx					
Subtask 2:					

In addition, we note that the inhaler used in the final formative study and the validation study contained a label that is affixed directly on the side of the dose cap that instructs patients to close the cap between doses. It is unclear whether this label will be present on the to-be marketed inhaler, if yes, clarify whether this was evaluated in your human factors validation testing. Provide clarification to address the above concerns, and submit a sample of the inhaler. If the information will not be listed on the dose cap, provide your justification for discrepancy noted.

Provide your responses to the requests by email to Sadaf.nabavian@fda.hhs.gov by COB Thursday, June 15, 2017. Your responses must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Sadaf Nabavian, Regulatory Health Project Manager, at 301-796-2777.

Review/History Clearance

Drafted by: SNabavian (for L. Musse)/6.12.2017
Clearance: SBarnes/6.12.2017
Finalized: SNabavian/6.12.2017

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/s/

SADAF NABAVIAN
06/12/2017

NDA 207921
QVAR Redihaler (beclomethasone dipropionate inhalation aerosol)
Norton Waterford Limited

Your submission dated October 1, 2016, for QVAR REDIHALER (beclomethasone dipropionate inhalation aerosol) is currently under review. The following comment provides clarification as to some of the changes made in the attached label. The FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

- We acknowledge that you have used the QVAR package insert as a guide for your proposed QVAR REDIHALER package insert, however, the package inserts for inhaled corticosteroids (ICS) have since evolved . In order to provide information in the most current format, we are providing our proposed labeling revisions consistent with the current format, of your recently approved product, ArmonAir RespiClick. Other revisions (specifically to the Dosage and Administration section) are concurrently being incorporated as part of NDA 020911/ S-029. Comments as they apply are included throughout the package insert.

Submit revised labeling incorporating the changes shown in the attached marked up labels via email to Sadaf.Nabavian@fda.hhs.gov by COB, June 14, 2017, followed by official submission to the supplemental NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

(See appended electronic signature)

_____
Sadaf Nabavian, PharmD
Sr. Regulatory Project Manager

Drafted by: SNabavian/6.6.2017
Cleared by: LJafari/6.6.2017
Finalized by: SNabavian/6.6.2017

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/s/

SADAF NABAVIAN
06/06/2017

NDA 207921
beclomethasone dipropionate
Teva

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: May 30, 2017

To: Arthur Merlin Destreux, M.S. Associate Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 610-786-7051	**Fax number:** (301) 796-9728
Phone number: 610-727-6125	**Phone number:** (240) 402-3720

Subject: NDA 207921 (beclomethasone dipropionate) Information Request

Total no. of pages including cover: 3

Comments: Please confirm receipt at laura.musse@fda.hhs.gov

Document to be emailed to: Arthur.MerlinDestreux@tevapharm.com (Secured email)

NDA 207921
beclomethasone dipropionate
Teva

Your submission, dated October 3, 2016 to NDA 207921, is currently under review. We have the following comments and requests for information:

As report QDP0087480 (module 3.2.p.2.4 Extractable And Leachables - Introduction) stated that a correlation between extractables and leachables levels could not be established. Therefore the leachables in the drug product and extractables from critical device components should be monitored for quality control.

- For the extractables from the [redacted] (b) (4) were described in report QDP0087480 based on [redacted] (b) (4) per day. The levels of [redacted] (b) (4) the SCT. Provide an explanation as to why these were not chosen as candidates for monitoring in the leachable studies.

- The Leachables studies were not described consistently among report QDP0087480 (pg 39), NCL0005307 in module 4.2.3.7.7 (pg. 5), and QDP108383 and 108389 in module 3.2.P.8.3 (leachables assessment – exhibit [redacted] (b) (4) mcg and [redacted] (b) (4) mcg, pg.7) regarding the orientation and length of the studies. Clarify your final plan and if and when 15-, 18-, or 24-month time points are available for products stored under controlled room temperature (25 ± 2°C/60 ± 5% relative humidity).

Please provide a response to the request by email (Laura.Musse@fda.hhs.gov) by COB on Friday, June 30, 2017. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance

Drafted by: L. Musse:	Date: 5/30/17
Clearance: S. Barnes:	Date: 5/30/17
Finalized: L. Musse:	Date: 5/30/17
File Name: Nonclinical IR:	Date: 5/30/17

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/s/

LAURA MUSSE
05/30/2017

From: Aisida, Bamidele (Florence)
To: "Arthur Merlin Destreux"
Cc: Musse, Laura
Subject: NDA 207921 IR 5-16-17
Date: Tuesday, May 16, 2017 11:24:02 AM

Dear Arthur,

Please respond to the following with a submission to your NDA by Tuesday, May 23, 2016.

1. For the Height Check measurement and the [redacted] (b) (4) defect test procedures, provide the acceptance criteria, data which justify the proposed ranges, the dimensions of the test units and justification for their dimensions, and the frequency of calibration of the [redacted] (b) (4) unit.

2. Provide the test methods to your Batch Manufacturing Records for measuring [redacted] (b) (4), [redacted] (b) (4).

3. To lower the risk of damaging the valve [redacted] (b) (4) insert explicit instructions with acceptance criteria into your Batch Manufacturing Records for setting the [redacted] (b) (4) [redacted] (b) (4)

4. The executed batch records for registration batches RD1504 and RD1505, and Table 12 in the file *manuf-proc-devel.pdf*, show a target [redacted] (b) (4). Table 4 in the file *manuf-process-and-controls.pdf* (Section 3.2.P.3.3 *Manufacture*) lists the [redacted] (b) (4) Reconcile these different values for [redacted] (b) (4) and insert the correct value in all instances in your application where appropriate. Provide a list of all relevant changes to your application.

5. [redacted] (b) (4)

6.

7.

(b) (4)

Provide individual unit APSD and Delivered Dose Uniformity data from full-scale manufacturing batches at the beginning-, middle- and end-of-batch to demonstrate that changes in these parameters are acceptable.

8. (b) (4)

Please confirm receipt of this email.

Thanks,

-Florence

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA. T: 240.402.2691

NDA 207921
beclomethasone dipropionate
Teva

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: March 10, 2017

To: Arthur Merlin Destreux, M.S. Associate Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 610-786-7051	**Fax number:** (301) 796-9728
Phone number: 610-727-6125	**Phone number:** (240) 402-3720

Subject: NDA 207921 (beclomethasone dipropionate) Information Request

Total no. of pages including cover: 3

Comments: Please confirm receipt at laura.musse@fda.hhs.gov

Document to be emailed to: Arthur.MerlinDestreux@tevapharm.com (Secured email)

NDA 207921
beclomethasone dipropionate
Teva

Your submission, dated October 3, 2016 to NDA 207921, is currently under review. We have the following comments and requests for information:

The report # QDP0108941, titled "Safety Assessment of Chemical Extractables from the [redacted] will need to be updated. The report was finalized on December, 2010 based on a maximum dose of [redacted] actuations per day. Since the current marketing proposal is for a maximum dose of [redacted] actuations per day, the new analytical evaluation threshold (AET) will be [redacted] of the original final AET. Submit an updated report to reflect this change. Accordingly any chemicals over the new AET should be listed for toxicity evaluation.

Additionally, in this report, an unknown [redacted] was mentioned. The reported level was [redacted] actuations per day for a 50kg person. This exceeds the SCT (0.15 ug/day) and QT [redacted] Using the recommendations from the document titled "Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products (PQRI, 2006)", the structure of the unknown [redacted] should be identified and submitted to QSAR per the ICH M7 (R1) Guidance. If it is QSAR positive, the levels should either be lowered to [redacted] µg/day or alternatively qualified as described in the ICH M7 (R1) Guidance. If the QSAR is negative, the levels should be either lowered to [redacted] µg/day, qualified in an appropriately designed 3-month inhalation toxicology study in a single species, or justified based on the published scientific literature demonstrating that this level poses no safety concerns to human subjects.

Please provide a response to the request by email (Laura.Musse@fda.hhs.gov) by COB on Tuesday, April 4, 2017. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance

Drafted by: L. Musse:	Date: 3/8/17
Clearance: S. Barnes:	Date: 3/10/17
Finalized: L. Musse:	Date: 3/10/17
File Name: Nonclinical IR:	Date: 3/10/17

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/s/

LAURA MUSSE
03/10/2017

From: Aisida, Bamidele (Florence)
To: "Arthur Merlin Destreux"
Cc: Musse, Laura
Subject: NDA 207921 IR
Date: Tuesday, February 21, 2017 2:09:48 PM

Dear Arthur,

Please respond to the following with a submission to your NDA by Tuesday, March 7, 2016.

1. Section 3.2.P.2.5 Pharmaceutical Development includes the statement that "the finished drug product will be tested for microbial content as per test method Microbiological Examination of Nonsterile Inhalation product as part of release testing and subsequent stability evaluation;" however, there is no such statement in Section 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment. It is unclear if Microbial Examination testing will be performed as part of the post-approval stability protocol. Clarify whether microbiological examination of the product will be performed as part of the post-approval stability protocol. If so, indicate the method and time points for testing.

2. We note that in your proposed commercial manufacturing batch records and other related documents, there are many places where the word (b) (4) appears in which you are apparently referring to a (b) (4). Substitute the word (b) (4) in all instances where the word (b) (4) is used incorrectly in both your batch records and all referenced or associated documents. Submit the corrected documents and batch records to your application with the itemized changes listed. In addition, list in the response to this request any instances in which the word (b) (4) is used and is not changed.

Please confirm receipt of this email.

Thanks,

-Florence

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA. T: 240.402.2691

NDA 207921
beclomethasone dipropionate
Teva

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: January 17, 2017

To: Arthur Merlin Destreux, M.S. Associate Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 610-786-7051	**Fax number:** (301) 796-9728
Phone number: 610-727-6125	**Phone number:** (240) 402-3720

Subject: NDA 207921 (beclomethasone dipropionate) Information Request

Total no. of pages including cover: 3

Comments: Please confirm receipt at laura.musse@fda.hhs.gov

Document to be emailed to: Arthur.MerlinDestreux@tevapharm.com

Your submission, dated October 3, 2016 to NDA 207921, is currently under review. We have the following comments and requests for information:

1. For studies 304, 301, 30039, and 302, generate tables of the baseline asthma therapy by drug class and treatment arm.

2. Include all randomized patients.

3. Provide executable SAS syntax, and either an RTF or MS Word version of the resulting tables. Refer to table example below:

Example table: Study 304 baseline asthma medications by therapeutic class:

	BAI 160		BAI 80		Placebo		All	
	N	(%)	N	(%)	N	(%)	N	(%)
Inhaled corticosteroids (ICS)								
Combination inhaled corticosteroids/long-acting beta agonists (ICS/LABA)								
Leukotriene modifiers								
Xanthines								
Anticholinergics								
Biologics								
Oral corticosteroids (OCS)								

Please provide a response to the request by email (Laura.Musse@fda.hhs.gov) by COB on Tuesday, January 24, 2017. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Health Project Manager, at 240-402-3720.

Review/History Clearance

Drafted by: L. Musse:	Date: 1/17/17
Clearance: S. Barnes:	Date: 1/17/17
Finalized: L. Musse:	Date: 1/17/17
File Name: Clinical IR:	Date: 1/17/17

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/s/

LAURA MUSSE
01/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207921

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Norton (Waterford) Limited
c/o Teva Branded Pharmaceutical Products R&D Inc.
41 Moores Road
Frazer, PA 19355

ATTENTION: Arthur Merlin d'Estreux, MS
Associate Director, Global Regulatory Affairs

Dear Mr. d'Estreux:

Please refer to your New Drug Application (NDA) dated October 1, 2016, received October 3, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Beclomethasone Dipropionate Breath-Actuated Inhalation Aerosol, 40 mcg and 80 mcg per actuation.

We also refer to your October 1, 2016, correspondence, received October 3, 2016, requesting review of your proposed proprietary name, Qvar RediHaler.

We have completed our review of the proposed proprietary name, Qvar RediHaler and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Laura Musse, Regulatory Project Manager in the Office of New Drugs, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
12/19/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207921

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Norton (Waterford) Limited
c/o Teva Branded Pharmaceutical Products R&D Inc.
41 Moores Road
Frazer, PA 19355

Attention: Arthur Merlin d'Estreux
Associate Director, Regulatory Affairs
Respiratory and Oncology

Dear Mr. d'Estreux:

Please refer to your New Drug Application (NDA) dated October 1, 2016, received October 3, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for QVAR REDIHALER, beclomethasone dipropionate, aerosol, metered inhalation, 40 – 320 mcg.

We also refer to your amendments dated October 4, and October 27, November 8, 20 and 23, and December 7, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is August 3, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 30, 2017.

During our filing review of your application, we identified the following potential review issues:

1. The results of study 302 in pediatric patients age 4 to 11 are noted. The adequacy of the efficacy data to support an indication in pediatric patients will be a review issue.

We are providing the above comment to give you preliminary notice of a potential review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to this issue during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. Provide clarification that the Summary of Clinical Efficacy (with included hyperlinks) is intended to serve as the Integrated Summary of Efficacy (ISE). Alternatively submit the ISE or provide its location within the NDA.

Please respond only to the above request for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable).

Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

If you have any questions, contact Laura Musse, Regulatory Health Project Manager, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
12/15/2016

NDA 207921
beclomethasone dipropionate
Teva

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 20, 2016

To: Arthur Merlin Destreux, MS Associate Director, Global Regulatory Affairs	**From:** Laura Musse, RN, MS, CRNP Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 610-786-7051	**Fax number:** (301) 796-9728
Phone number: 610-727-6125	**Phone number:** (240) 402-3720

Subject: NDA 207921 (beclomethasone dipropionate) Information Request

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at laura.musse@fda.hhs.gov

Document to be emailed to: Arthur.MerlinDestreux@tevapharm.com

NDA 207921
beclomethasone dipropionate
Teva

Your submission, dated October 3, 2016 to NDA 207921, is currently under review. We have the following requests for information:

1. Confirm if the beclomethasone dipropionate breath actuated inhaler drug product tested in Study BDB-AS-101will be the same as the to-be-marketed beclomethasone dipropionate breath actuated inhaler drug product.

2. Provide the batch size of the beclomethasone dipropionate breath actuated inhaler drug product tested in Study BDB-AS-101, relative to the batch size of the to-be-marketed beclomethasone dipropionate breath actuated inhaler drug product.

3. Indicate if the U.S. approved and marketed beclomethasone dipropionate metered-dose inhaler drug product (QVAR) was used to conduct Study BDB-AS-101.

Please provide a response to the requests by email (Laura.Musse@fda.hhs.gov) or facsimile (301-796-9728), by Friday, November 25, 2016. Your response must also be submitted formally to the IND shortly thereafter. If you have any questions, please contact Laura Musse, Regulatory Project Manager, at 240-402-3720.

Review/History Clearance

Drafted by: L. Musse:	Date: 11/18/16
Clearance: S. Barnes:	Date: 11/18/16
Finalized: L. Musse:	Date: 11/20/16
File Name: ClinPharm IR:	Date: 11/18/16

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/s/

LAURA MUSSE
11/20/2016

NDA 207921
beclomethasone dipropionate
Teva

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 27, 2016

To: Arthur Merlin Destreux, MS Associate Director, Global Regulatory Affairs	**From:** Brandi Wheeler, PharmD Regulatory Health Project Manager
Company: Teva Branded Pharmaceutical Products R&D Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 610-786-7051	**Fax number:** (301) 796-9728
Phone number: 610-727-6125	**Phone number:** (301) 796-4495

Subject: NDA 207921 (beclomethasone dipropionate) Information Request

Total no. of pages including cover: 3

Comments: Please respond by November 10, 2016

Document to be emailed to:

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We are currently reviewing your New Drug Application (NDA), dated October 3, 2016 and have the following requests for information:

1. Provide all programs and underlying macros used to analyze change from baseline trough morning FEV1 AUEC from time zero to the end of treatment period in trials 304, 30039, 301

2. Provide all programs and underlying macros used to analyze change from baseline in the weekly average of daily trough morning PEF over the treatment period in trials 304, 30039, 301 and 302.

3. Provide all programs and underlying macros used to analyze change from baseline in the weekly average of daily trough evening PEF over the treatment period in trials 304, 301 and 302.

4. Provide all programs and underlying macros used to analyze change from baseline in trough morning FEV1 over the treatment period in trial 302.

5. Provide all programs and underlying macros used to analyze change from baseline in the weekly average of daily trough morning FEV1 by handheld spirometer over the treatment period in trial 30039.

6. Provide all programs and underlying macros used to analyze change from baseline in the weekly average of total daily use of albuterol/salbutamol inhalation aerosol over the treatment period in trials 304, 30039, 301 and 302.

7. Provide all programs and underlying macros used to analyze change from baseline in the weekly average of total daily asthma symptom score over the treatment period in trials 304, 30039, 301 and 302.

8. Provide all programs and underlying macros used to analyze time to patient withdrawal for worsening asthma during the treatment period in trials 304, 30039, 301 and 302.

9. Provide programs of major safety analyses on integrated set of studies 304, 30039 and 301.

Please provide a response to the requests by email (Brandi.Wheeler@fda .hhs.gov) or facsimile (301-796-9728), by 4 pm on Thursday, November 10, 2016. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

NDA 207921
beclomethasone dipropionate
Teva

Drafted by: M Xi 10/26/16 / G Levin 10/26/16
B Wheeler 10/26/16

Cleared by: S Barnes 10/27/16

Finalized by: B Wheeler 10/27/ 16

NDA 207921
beclomethasone dipropionate
Teva

Review/History Clearance

Drafted by: L. Musse:	Date: 10/X/16
Clearance: S. Barnes:	Date: 10/X/16
Finalized: L. Musse:	Date: 10/X/16
File Name: Clinical IR:	Date: 10/X/16

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/s/

BRANDI E WHEELER
10/27/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207921

NDA ACKNOWLEDGMENT

Norton (Waterford) Limited
c/o Teva Branded Pharmaceutical Products R&D Inc.
41 Moores Road
Frazer, PA 19355

Attention: Arthur Merlin d'Estreux

Dear Mr. d'Estreux:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: beclomethasone dipropionate, inhalation aerosol, 40 mcg, 80 mcg

Date of Application: October 3, 2016

Date of Receipt: October 3, 2016

Our Reference Number: 207921

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 2, 2016 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3) . The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Laura Musse, R.N., M.S., C.R.N.P.
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LAURA MUSSE
10/21/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114865

MEETING MINUTES

Teva Branded Pharmaceutical Products R&D, Inc.
74 NW 176th Street
Miami, FL 33169

Attention: Jacqueline Howard
Manager, Regulatory Affairs

Dear Ms. Howard:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Beclomethasone Dipropionate HFA Breath-Actuated Inhalation Aerosol (BDP HFA BAI).

We also refer to the telecon between representatives of your firm and the FDA on April 28, 2015. The purpose of the meeting was to discuss the submission of a New Drug Application for BDP HFA BAI for maintenance treatment of asthma in patients 4 years of age and older.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	April 28, 2015; 3:00 – 4:00 PM EST
Application Number:	IND 114865
Product Name:	Beclomethasone Dipropionate HFA Breath-Actuated Inhalation Aerosol (BDP HFA BAI)
Indication:	Asthma
Sponsor Name:	Teva Branded Pharmaceutical Products R&D, Inc.
Meeting Chair:	Badrul A. Chowdhury
Meeting Recorder:	Nina Ton

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Banu Karimi-Shah, MD, Clinical Team Leader, DPARP
Miya Paterniti, MD, Clinical Reviewer, DPARP
Marcie Wood, PhD, Pharmacology/Toxicology Supervisor, DPARP
Carol Galvis, PhD, Pharmacology/Toxicology Reviewer, DPARP
Yunzhao Ren, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Craig Bertha, PhD, CMC Lead, Division of New Drug Products Branch IV, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
David Petullo, MS, Biostatistics Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
Kiya Hamilton, PhD, Biostatistics Reviewer, Division of Biometrics II, OB
Brandi Wheeler, PharmD, Regulatory Project Manager, DPARP
Nina Ton, PharmD, Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Tushar P. Shah, MD, Senior Vice President, Teva Global Respiratory R&D
Calvin Small, MD, MS, Director, Clinical Research, Teva Global Respiratory R&D
Sinead Kavanagh, Senior Regulatory Affairs Officer, Pharmaceutical Development, Teva Global Respiratory R&D

Declan Walsh, Principal Device Engineer, Pharmaceutical Development, Teva Global Respiratory R&D
Julian Blair, PhD, CChem, MRSC, Senior Director, Pharmaceutical Development, Teva Global Respiratory R&D
Yu Ru, MBA, MS, PMP, Project Champion, Respiratory Project Management, Teva Global Respiratory R&D
Stephanie Dunbar, PhD, Head of Global Statistics, Teva Global R&D
Mary McKenry, PhD, Principal Statistician, Biostatistics and Data Management, Teva Global Respiratory R&D
Jacqueline Howard, Manager, Global Regulatory Affairs, Teva Global Respiratory R&D
Sandra Anderson, MJ, RAC, Associate Director, Regulatory Affairs, Teva Global Respiratory R&D
Steve Viti, PhD, MBA, Senior Director, Global Regulatory Affairs, Teva Global Respiratory R&D

1. BACKGROUND

Teva submitted a Type B meeting request dated February 17, 2015, to the Division of Pulmonary, Allergy, and Rheumatology Products to discuss the submission of a New Drug Application for BDP HFA BAI for maintenance treatment of asthma in patients 4 years of age and older. Upon review of the meeting package, the Division provided preliminary comments to Teva's questions via electronic correspondence on April 22, 2015. Jacqueline Howard, Teva's Regulatory Affairs Manager, communicated to the Division via email dated April 24, 2015, that the Sponsor requested to change the meeting format to a teleconference and will focus the meeting discussion to clinical questions 1 and 2. In addition, Teva provided clarification questions to the FDA Preliminary Comments. Teva's questions and clarification questions are in *italics*, FDA's responses are in normal font, and the meeting discussion is in **bold**.

2. DISCUSSION

CLINICAL

Question 1

Study 304 demonstrated a significant difference from placebo for the primary outcome variable (change from baseline in forced expiratory volume in 1 second [FEV1]) and the secondary outcome measures were generally supportive. Study 301 did not demonstrate a significant difference from placebo for the primary outcome variable (change from baseline in FEV1) for any of the treatment groups including both BAI and MDI strengths; however, there were substantial improvements observed for secondary efficacy measures ($p<0.05$). (b) (4), which was conducted previously with an earlier version of the BAI device and the marketed QVAR canister, demonstrated significant improvements in the primary efficacy measure (baseline-adjusted percent-predicted maximum FEV1 after 12 weeks) with secondary outcome measures that were also supportive for both BDP BAI and BDP MDI relative to placebo and provides additional supportive efficacy data. Does the Agency agree that the results from Study 301,

along with positive results from Study 304 [redacted] provide adequate support for approval of the NDA?

- *If FDA's response to Clinical Question 1 is positive with regard to Studies 301, 304, [redacted] being sufficient to support the submission of an NDA, then please also respond to all included Statistical Questions, CMC Questions, and Regulatory/Electronic Submission Questions. A response to Clinical Question 2 is not necessary.*

- *If FDA's response to Clinical Question 1 is that FDA recommends Teva conduct an additional clinical study, then please respond to Clinical Question 2, CMC Question 2, and Regulatory/Electronic Submission Questions 1 and 2 below. FDA no longer needs to respond to Statistical Questions 1, 2, 3, 4, and 5 and CMC Question 1.*

FDA Response

We do not agree. A key objective of the clinical development program is to establish the efficacy, safety, and usability of the new Redihaler Device. [redacted]

Clarification regarding Clinical Question 1

Teva would like to know if demonstration of in vitro bioequivalence between the three QVAR Redihaler exhibit batches [redacted] using the MDI in-vitro tests required as per the Draft Guidance on Albuterol Sulfate, would allow the FDA to reconsider their position on this response and allow Teva to use Clinical [redacted] along with Clinical Studies 301 and 304 to provide adequate support for approval of the NDA? The proposed in-vitro tests as outlined in the guidance are Single Actuation Content (SAC), APSD based on ISM, Spray Pattern and Plume Geometry, Priming and Repriming.

In the event the FDA does not agree that this is a viable option or if we cannot demonstrate in vitro equivalence, then Teva would be prepared to proceed with the recommended additional study. In that event we have three further clarifying questions below.

Meeting Discussion

FDA does not agree with Teva's proposal to demonstrate in vitro bioequivalence because there are no established standards on how to define for in vitro bioequivalence.

Question 2

If the application is not supported by the current study results, Teva proposes to conduct another placebo-controlled study of 6-weeks duration evaluating the BAI at the 320 and 640 mcg/day doses only and not to include the reference MDI arms. Does the Agency agree that this additional study, when successfully completed, would be adequate to support the approval of the NDA?

FDA Response

A 6-week trial duration is acceptable. Your clinical development program relies on the benchmark comparison to the current QVAR press-and-breathe device, and therefore these treatment arms should be included in this study, not only to provide a reference, but also to establish assay sensitivity. If successfully completed, we agree that this additional study would be adequate to support your NDA submission.

Clarifications regarding Clinical Question 2

(a) *If Teva agrees to proceed with an additional pivotal study with the MDI included as a comparator, as recommended by the FDA, Teva would like to propose a 4-week study instead of a 6-week study duration. The justification for this is that the effect of ICS treatment has been shown to peak at approximately 3 weeks and then plateau with ongoing therapy, and safety over 12 weeks has already been demonstrated in Studies 301 and 304 for Qvar RediHaler. A four week duration of treatment for ICS containing product as being adequate to assess efficacy is further supported by The FDA's Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate generic product development where a 4-week treatment duration is considered to be adequate to assess the comparative efficacy of the test and reference products. The other benefit of a shorter treatment duration is that the impact of withdrawals on the statistical analysis of the primary efficacy measure will be minimized.*

Based on the above justification, would FDA agree that a 4-week study is sufficient to establish comparable efficacy between Qvar MDI and Qvar Redihaler?

Meeting Discussion

Additionally, Teva reasoned that two 12-week studies have been conducted with the new device and that a 4-week study would be adequate to evaluate the true life exposure of the device. FDA understood Teva's rationale for proposing a 4-week study; however, FDA recommended a 6-week study to have consistency across all inhaled corticosteroid development programs.

Clarifications regarding Clinical Question 2

(b) *Teva proposes a study design to include beclomethasone dipropionate (BDP) metered dose inhaler (MDI) reference arm at the 320 mcg/day strength in order to serve as a positive control and a reference to the two breath actuated inhaler (BAI) treatment arms.*

Justification: Teva acknowledges the FDA feedback regarding need to include an MDI treatment arm in the study to serve as reference and establish assay sensitivity. Teva has conducted two clinical trials comparing two doses of BDP BAI to MDI. In each trial, no clinical differences in efficacy were observed between the HFA MDI and BAI treatments and as expected no evidence for dose response was observed between the two strengths of each product. The inability to demonstrate dose response to ICS is well established and is the basis for the recent change in FDA requirements for development of generic ICS containing products where a four week clinical trial comparing the lowest strength/dose is considered adequate for demonstrating comparable efficacy. Consistent with this understanding, Teva proposes to include the 160mcg twice daily (320mcg daily dose) as the only HFA MDI comparator in the trial. This will serve as a positive control for purpose of supporting assay sensitivity and as a reference arm to the

160mcg and 320mcg twice daily BAI treatment arms. Since separation in two doses of the HFA MDI on clinical efficacy measures is extremely unlikely and demonstration of efficacy for the HFA MDI product which is currently approved is not the objective of the BDP BAI development program, the inclusion of the low strength will address the Agency's needs and allow Teva to conduct the study in the most cost effective manner. Additionally, in the prior study (BDB-AS-301), patients were required to take 4 inhalations from the HFA MDI and BAI devices (8 inhalations total) each morning and each evening. As such, one explanation for the lack of study success in 301 is that this cumbersome regimen could have impacted patient adherence to therapy. By removing one of the treatment arms, patients would now have to administer 6 inhalations twice daily which helps to simplify the treatment regimen if a double dummy design is utilized. The proposed treatments for the new study are as follows:

BDP BAI 4 inhalations (40 mcg/inhalation) twice daily, plus MDI placebo 2 puffs twice daily
BDP BAI 4 inhalations (80 mcg/inhalation) twice daily, plus MDI placebo 2 puffs twice daily
BDP BAI Placebo 4 inhalations twice daily, plus BDP MDI 2 puffs (80 mcg/inhalation) twice daily
BAI Placebo 4 inhalations twice daily, plus MDI placebo 2 puffs twice daily

By using this design, the double blind, double-dummy configuration would be maintained, while minimizing the total number of inhalations required. Teva would also like to suggest a further simplification of the treatment regimen which forms the basis for the next question.

Does the FDA agree that the use of only one MDI reference arm at 320 mcg/day strength is sufficient for the proposed study?

Meeting Discussion
FDA agreed to the use of only one MDI reference arm at 320 mcg/day.

Clarifications regarding Clinical Question 2
(c) *Teva proposes an alternative study design that would minimize the number of inhalations for any patient.*

Justification: We propose to remove the double-dummy aspect of the study design. This alternative study design will allow to assess the efficacy of both 320 mcg/day and 640 mcg/day doses from BDP BAI and the 320 mcg/day HFA MDI doses in a blinded manner. This design will still address the Agency's need to include a reference arm to serve as a positive control; however, this will be achieved with the minimal number of inhalations and number of devices to be used twice daily. The treatment groups would be as follows:

BDP BAI 320 mcg/day, 4 inhalations (40 mcg/inhalation) twice daily
BDP BAI 640 mcg/day, 4 inhalations (80 mcg/inhalation) twice daily
BDP MDI 320 mcg/day, 4 inhalations (40 mcg/inhalation) twice daily
BAI placebo 4 inhalations twice daily
MDI placebo 4 inhalations twice daily

This design will maintain the double blind nature of the study while more closely resembling how the product will be used once approved and will be much less burdensome and complex for the patients who participate in the study thereby reducing the possibility of poor adherence confounding the outcome of the trial.

Does the FDA agree with this alternate proposed study design to simplify the patient dosing?

Meeting Discussion
FDA agreed with the proposal to remove the double-dummy design from the study.

STATISTICS

Question 1
Since the 2 pivotal studies have no common dose regimens, Teva does not intend to pool efficacy data across any of the studies. Primary support for efficacy will be provided by side-by-side presentations of the efficacy endpoints in the 2 pivotal studies (Studies 301 and 304) and with results from (b) (4) *summarized separately. It is our intention to summarize the clinical studies in Section 2.7.3 Summary of Clinical Efficacy in accordance with NDA regulations 21 Code of Federal Regulations (CFR) 314.50(d)(5)(v) and meet the prescribed size limitations for Module 2 and not produce a separate Integrated Summary of Efficacy. Does the Agency agree with this approach?*

FDA Response
Response not necessary given response to Clinical Question 1.

Meeting Discussion
This question was not discussed.

Question 2
It is proposed that the Integrated Summary of Safety (ISS) will include a pooling of active treatment arms from the 12-week double-blind efficacy studies 301 and 304 only for use in subgroup analyses. Safety results from (b) (4) *will be summarized separately. Does the Agency agree with the proposed ISS approach?*

FDA Response
Response not necessary given response to Clinical Question 1.

Meeting Discussion
This question was not discussed.

Question 3
Teva proposes to analyze data from Studies 304 and 301 using the following subgroups:

- *Sex (Male/Female) (Efficacy and Safety)*
- *Age (12 to 17, 18 to 64, and ≥65 years) (Efficacy and Safety)*
- *Race (white, black, and all other races) (Efficacy and Safety)*
- *US versus non-US (Safety only)*

Does the Agency agree with this approach?

FDA Response
Response not necessary given response to Clinical Question 1.

Meeting Discussion
This question was not discussed.

Question 4
Teva proposes that if datasets are submitted electronically in the NDA in accordance with Clinical Data Interchange Standards Consortium (CDISC) standards, individual patient profiles are not necessary. Does the Agency agree with this proposal?

FDA Response
Response not necessary given response to Clinical Question 1.

Meeting Discussion
This question was not discussed.

Question 5
Teva proposes to only submit case report forms (CRFs) for adverse events leading to withdrawal, deaths, and serious adverse events (SAEs). Does the Agency agree that this is sufficient?

FDA Response
Response not necessary given response to Clinical Question 1.

Meeting Discussion
This question was not discussed.

CMC

Question 1

Stability testing is underway on 3 exhibit batches per product strength (40 mcg/80 mcg); the 12-month testing is complete with all data generated at controlled room temperature (CRT) stability storage conditions meeting specification. Three distinct lots of "primeless" (b) (4) valves were used to manufacture the exhibit stability and clinical supplies. During testing of the 6-month 40°C/75% relative humidity (RH) samples, (b) (4) (b) (4) The problem was evident at higher temperature conditions and was prevalent, in particular, in 1 lot of the valve (used to make 1 batch each of low- and high-strength product). A detailed investigation followed in partnership with (b) (4) the valve manufacturer. Particular attention was given to the (b) (4)

Based on this situation, Teva is proposing the following approach to satisfy the stability requirements for submission:

- *Teva will submit in the NDA 6 months of accelerated (ACC)/intermediate (INT) and 12 months of CRT stability data on 3 exhibit stability batches of each strength at CRT-manufactured with valves using the original valve (b) (4)*

- *In addition, Teva will manufacture 3 new stability batches of each strength incorporating the improved valve seal manufacturing process and will submit in the NDA 3 months ACC and long-term stability data from these new stability batches and amend the NDA no later than 4 months into the review period with 6 months ACC and CRT stability data.*

Does the Agency find this approach acceptable?

FDA Response

Response not necessary given response to Clinical Question 1.

Meeting Discussion

This question was not discussed.

Question 2

Teva will manufacture the canister with a printed batch number and apply the batch number directly onto the actuator label without the need for a label on the canister. The actuator will be sealed so that the patient cannot disassemble and remove the canister. Does the Agency find it acceptable that the canister will not be labelled?

FDA Response
Yes, we find it acceptable, considering your claims that the patient will not be able to remove the canister and that you will include pertinent identification information (batch and canister numbers) in both data matrix and human readable form.

Meeting Discussion
This question was not discussed.

REGULATORY/ELECTRONIC SUBMISSION

Question 1
Teva proposes to place the IFU Label Comprehension sub-study of Study 304 in Module 1.14.1.4. Does the Agency agree that this is the appropriate placement in the eCTD structure of the NDA?

FDA Response
Please contact ESUB@fda.hhs.gov for the placement of the above study in the eCTD structure of the NDA.

Meeting Discussion
This question was not discussed.

Question 2
The sole Reference Product for the QVAR Breath Actuated Inhalation (BAI) 505(b)(2) submission will be QVAR Inhalation Aerosol. Does the Agency agree with this proposal?

FDA Response
The Agency normally does not advise a sponsor on the selection of a particular listed drug that may be relied upon to support approval of a proposed product. An exception is that if there is a listed drug that is a pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, that drug should be identified as the listed drug. A sponsor interested in submitting a 505(b)(2) application that relies upon the Agency's finding of safety and/or effectiveness for a listed drug should determine which listed drug(s) is/are the most appropriate for their development plan. Refer to the 505(b)(2) REGULATORY PATHWAY section below.

Meeting Discussion
This question was not discussed.

3. ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any

published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is

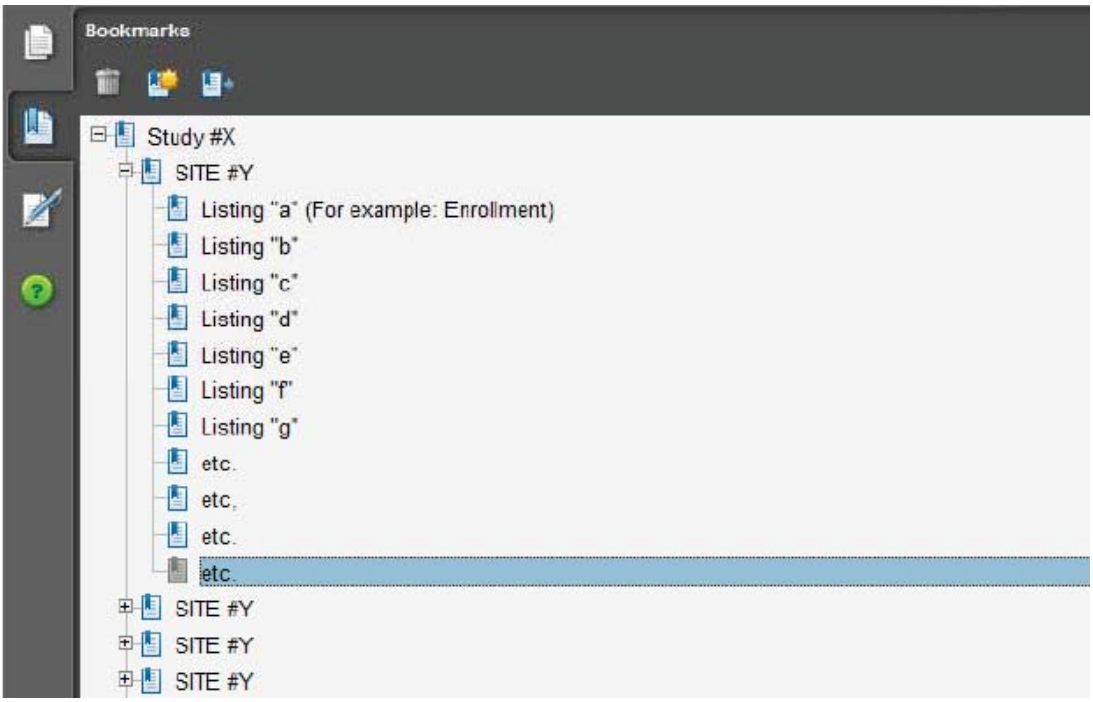
maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

4. ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

5. ACTION ITEMS
There were no action items.

6. ATTACHEMENT OR HANDOUTS
Teva's clarification questions are attached.

Teva's Pre NDA Meeting Clarification Questions to FDA Comments on the Briefing Document.
(There is one clarification question regarding FDA response #1 and three clarification questions regarding FDA response #2).

Clarification regarding Clinical Question #1

Teva would like to know if demonstration of in vitro bioequivalence between the three QVAR Redihaler exhibit batches [redacted] (b) (4) using the MDI *in-vitro* tests required as per the *Draft Guidance on Albuterol* Sulfate, would allow the FDA to reconsider their position on this response and allow Teva to use Clinical [redacted] (b) (4) along with Clinical Studies 301 and 304 to provide adequate support for approval of the NDA? The proposed *in-vitro* tests as outlined in the guidance are Single Actuation Content (SAC), APSD based on ISM, Spray Pattern and Plume Geometry, Priming and Repriming.

In the event the FDA does not agree that this is a viable option or if we cannot demonstrate in vitro equivalence, then Teva would be prepared to proceed with the recommended additional study. In that event we have three further clarifying questions below.

Clarifications regarding Clinical Question 2

(a) If Teva agrees to proceed with an additional pivotal study with the MDI included as a comparator, as recommended by the FDA, Teva would like to propose a 4-week study instead of a 6-week study duration. The justification for this is that the effect of ICS treatment has been shown to peak at approximately 3 weeks and then plateau with ongoing therapy, and safety over 12 weeks has already been demonstrated in Studies 301 and 304 for Qvar RediHaler. A four week duration of treatment for ICS containing product as being adequate to assess efficacy is further supported by The FDA's *Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate* generic product development where a 4-week treatment duration is considered to be adequate to assess the comparative efficacy of the test and reference products. The other benefit of a shorter treatment duration is that the impact of withdrawals on the statistical analysis of the primary efficacy measure will be minimized.

Based on the above justification, would FDA agree that a 4-week study is sufficient to establish comparable efficacy between Qvar MDI and Qvar Redihaler?

(b) Teva proposes a study design to include beclomethasone dipropionate (BDP) metered dose inhaler (MDI) reference arm at the 320 mcg/day strength in order to serve as a positive control and a reference to the two breath actuated inhaler (BAI) treatment arms.

Justification: Teva acknowledges the FDA feedback regarding need to include an MDI treatment arm in the study to serve as reference and establish assay sensitivity. Teva has conducted two clinical trials comparing two doses of BDP BAI to MDI. In each trial, no clinical differences in efficacy were observed between the HFA MDI and BAI treatments and as expected no evidence for dose response was observed between the two strengths of each product. The inability to demonstrate dose response to ICS is well established and is the basis for the recent change in FDA requirements for development of generic ICS containing products where a four week clinical trial comparing the lowest strength/dose is considered adequate for demonstrating comparable efficacy. Consistent with this understanding, Teva proposes to include the 160mcg twice daily (320mcg daily dose) as the only HFA MDI comparator in the trial. This will serve as a positive control for purpose of supporting assay sensitivity and as a reference arm to the 160mcg and 320mcg twice daily BAI treatment arms. Since separation in two doses of the HFA MDI on clinical efficacy measures is extremely unlikely and demonstration of efficacy for the HFA MDI product which is currently approved is not the objective of the BDP BAI development program, the inclusion of the low strength will address the Agency's needs and allow Teva to conduct the study in the most cost effective manner. Additionally, in the prior study (BDB-AS-301), patients were required to take 4 inhalations from the HFA MDI and BAI devices (8 inhalations total) each morning and each evening. As such, one explanation for the lack of study success in 301 is that this cumbersome regimen could have impacted patient adherence to therapy. By removing one of the treatment arms, patients would now have to administer 6 inhalations twice daily which helps to simplify the treatment regimen if a double dummy design is utilized. The proposed treatments for the new study are as follows:

> BDP BAI 4 inhalations (40 mcg/inhalation) twice daily, plus MDI placebo 2 puffs twice daily
> BDP BAI 4 inhalations (80 mcg/inhalation) twice daily, plus MDI placebo 2 puffs twice daily
> BDP BAI Placebo 4 inhalations twice daily, plus BDP MDI 2 puffs (80 mcg/inhalation) twice daily
> BAI Placebo 4 inhalations twice daily, plus MDI placebo 2 puffs twice daily

By using this design, the double blind, double-dummy configuration would be maintained, while minimizing the total number of inhalations required. Teva would also like to suggest a further simplification of the treatment regimen which forms the basis for the next question. .

Does the FDA agree that the use of only one MDI reference arm at 320 mcg/day strength is sufficient for the proposed study?

(c) Teva proposes an alternative study design that would minimize the number of inhalations for any patient.

Justification: We propose to remove the double-dummy aspect of the study design. This alternative study design will allow to assess the efficacy of both 320 mcg/day and 640 mcg/day doses from BDP BAI and the 320 mcg/day HFA MDI doses in a blinded manner. This design will still address the Agency's need to include a reference arm to serve as a positive control; however, this will be achieved with the minimal number of inhalations and number of devices to be used twice daily. The treatment groups would be as follows:

BDP BAI 320 mcg/day, 4 inhalations (40 mcg/inhalation) twice daily
BDP BAI 640 mcg/day, 4 inhalations (80 mcg/inhalation) twice daily
BDP MDI 320 mcg/day, 4 inhalations (40 mcg/inhalation) twice daily
BAI placebo 4 inhalations twice daily
MDI placebo 4 inhalations twice daily

This design will maintain the double blind nature of the study while more closely resembling how the product will be used once approved and will be much less burdensome and complex for the patients who participate in the study thereby reducing the possibility of poor adherence confounding the outcome of the trial.

Does the FDA agree with this alternate proposed study design to simplify the patient dosing?

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

/s/

PHUONG N TON
05/15/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114865

MEETING MINUTES

Teva Branded Pharmaceutical Products R&D, Inc.
74 NW 176th Street
Miami, FL 33169

Attention: Jacqueline Howard
Manager, Regulatory Affairs

Dear Ms. Howard:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Beclomethasone Dipropionate HFA Breath-Actuated Inhalation Aerosol.

We also refer to the telecon between representatives of your firm and the FDA on October 6, 2014. The purpose of the meeting was to discuss the proposed phase 3 development program.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	October 6, 2014; 2:00 – 3:00 PM
Application Number:	IND 114865
Product Name:	Beclomethasone Dipropionate HFA Breath-Actuated Inhalation Aerosol
Indication:	Asthma
Sponsor Name:	Teva Branded Pharmaceutical Products R&D, Inc.
Meeting Chair:	Lydia Gilbert-McClain, MD
Meeting Recorder:	Nina Ton, PharmD

FDA ATTENDEES

Lydia Gilbert-McClain, MD, Deputy Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Banu Karimi-Shah, MD, Clinical Team Leader, DPARP
Miya Paterniti, MD, Clinical Reviewer, DPARP
Marcie Wood, PhD, Pharmacology/Toxicology Team Leader, DPARP
Satjit Brar, PhD, PharmD, BS, Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Thomas Permutt, PhD, Director, Division of Biometrics II, Office of Biostatistics (OB)
David Petullo, MS, Biostatistics Team Leader, Division of Biometrics II, OB
Kiya Hamilton, PhD, Biostatistics Reviewer, Division of Biometrics II, OB
Craig Bertha, PhD, Acting Team Leader, Division of New Drug Quality Assessment III, Office of New Drug Quality Assessment (ONDQA)
Nina Ton, PharmD, Regulatory Project Manager, DPARP
(b) (4)

SPONSOR ATTENDEES

Tushar P. Shah, MD, Senior Vice President, Teva Global Respiratory R&D
Christopher O'Brien, MD, PhD, FCCP, Vice President, Teva Global Respiratory R&D
Calvin Small, MD, MS, Director, Clinical Research, Teva Global Respiratory R&D
Stephanie Dunbar, Global Head, Statistics, Teva Branded Pharmaceutical Products R&D
Youyi Shu, PhD, Senior Director, Global Biostatistics, Teva Branded Pharmaceutical Products R&D

Julian Blair, PhD, CChem, MRSC, Senior Director, Pharmaceutical Development, Teva Global Respiratory R&D
Sinead Kavanagh, Senior Regulatory Affairs Officer, Pharmaceutical Development, Teva Global Respiratory R&D
Declan Walsh, Senior Device Engineer, Pharmaceutical Development, Teva Global Respiratory R&D
Yu Ru, MBA, MS, PMP, Senior Director Project Management, Teva Global Respiratory R&D
Steve Viti, PhD, MBA, Senior Director, Global Regulatory Affairs, Teva Global Respiratory R&D
Sandra Anderson, M.J., RAC, Associate Director, Global Regulatory Affairs, Teva Global Respiratory R&D
(b) (4)
Jacqueline Howard, Manager, Global Regulatory Affairs, Teva Global Respiratory R&D

1. BACKGROUND

Teva submitted a meeting request dated July 18, 2014, to the Division of Pulmonary, Allergy, and Rheumatology Products, to discuss the proposed phase 3 development program for Beclomethasone Dipropionate HFA Breath-Actuated Inhalation Aerosol for the treatment of asthma. Upon review of the meeting package, the Division provided preliminary comments via electronic correspondence on October 1, 2014. Jacqueline Howard, Teva's Manager, Regulatory Affairs, communicated to the Division via email dated October 3, 2014 that the Sponsor requested to change the meeting format from a face-to-face meeting to a teleconference. In addition, Teva requested to focus the meeting discussion to Questions 18 and 19, and also provided comments to FDA's responses for these questions. Teva's questions and comments to Questions 18 and 19 are in *italics*, FDA's responses are in normal font, and the meeting discussion is in **bold**.

2. DISCUSSION

CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

Question 1
Teva proposes to use a primeless valve for this product. Accordingly, there is no requirement for the patient to prime the inhaler prior to initial use, and after periods of non-use. Teva proposes to demonstrate this attribute in a priming/re-priming study with 1 resting time period of at least 2 weeks. Is the approach proposed acceptable?

FDA Response
Your proposal is acceptable.

Meeting Discussion
This question was not discussed.

Question 2
Teva proposes to adopt the same cleaning instructions for this product as for the QVAR metered-dose inhaler (MDI) product (ie, wipe the inhaler mouthpiece with a clean dry tissue or cloth weekly). Teva proposes to confirm this is acceptable in a cleaning study. Is the approach of confirming the suitability of the existing QVAR MDI cleaning instructions for BDP BAI acceptable?

FDA Response
Your proposal is acceptable.

Meeting Discussion
This question was not discussed.

Question 3
Teva performed a microbial challenge study in 2011 for the BDP Nasal Aerosol 80 mcg/actuation, 120 actuations product. As the microbial challenge study is related to the contents of the can, and the BDP BAI formulation is identical to the BDP Nasal formulation it is not considered necessary to repeat the study. Is the approach of using the existing microbial challenge study acceptable?

FDA Response
Your proposal is acceptable.

Meeting Discussion
This question was not discussed.

Question 4
Teva does not intend to market the BDP BAI product with a spacer or similar accessory as the inhaler is designed to eliminate the need to coordinate actuation and inhalation. However a study will be performed at flow rates of 15 L/min and 30 L/min to evaluate the BDP BAI product with a spacer. Is the approach for assessing the product with a spacer at flow rates of 15 L/min and 30 L/min acceptable?

FDA Response
Your approach is acceptable, and if it is determined that the BDP BAI drug product behaves unreliably with spacers, it may be necessary to include some warning language in the labeling.

Meeting Discussion
This question was not discussed.

Question 5
To acknowledge real life misuse scenarios the following protocol to investigate the effects of varying time delays on mouthpiece cover opening and closing is being proposed. Does the agency find this acceptable?

FDA Response
Your proposal is acceptable.

Meeting Discussion
This question was not discussed.

Question 6
As the product formulation is a solution, shaking is not required, however, to acknowledge real life misuse scenarios the effects of shaking during patient use will be evaluated. Does the agency find this approach acceptable?

FDA Response
Your proposal is acceptable.

Meeting Discussion
This question was not discussed.

Question 7
Due to the design of the primeless valve, inhaler orientation during the mouthpiece cover opening and closing does not affect the pharmaceutical performance of the product. The following study has been designed to investigate the potential real life scenarios in relation to inhaler orientation during patient use. Does the agency find this approach acceptable?

FDA Response
Your proposal is acceptable. However, clarify your proposed plan so that the orientation of the device during the wasting of doses just prior to the collection (one or two actuations) is also defined.

Meeting Discussion
This question was not discussed.

Question 8
Teva proposes to compare the in vitro performance of BDP BAI and QVAR MDI (without dose counter) by testing for delivered dose uniformity (DDU), APSD, spray pattern, and plume geometry. Is the approach for assessing in vitro comparability between both products acceptable?

FDA Response
Your proposal is acceptable, but such a comparison is not a requirement for establishment of quality.

Meeting Discussion
This question was not discussed.

Question 9
In addition to the range of stability and drug product characterization studies listed below (b) (4) (the valve manufacturer) shall submit a Drug Master File (DMF) detailing the valve design, operation and manufacture.

- *Priming/repriming*
- *Temperature cycling*
- *Dropping study*
- *Effect of time delay during patient use*
- *Effect of inhaler orientation during patient use*

Does the Agency agree that the range of studies conducted is sufficient to demonstrate the robustness and performance of the (primeless) valve used in this product?

FDA Response
The proposed studies appear to be acceptable. The demonstration of the robustness and performance of the (primeless) valve will be evaluated during review of the data provided.

Meeting Discussion
This question was not discussed.

Question 10
At the time of NDA submission, Teva will include (b) (4) months of stability for foreign particulates and will not have sufficient information to set acceptance criteria. Does the Agency agree that the NDA may be updated no later than (b) (4) months into the review period with additional stability data (12 months) and that the acceptance criteria be finalized no later than 1 year after launch on the market?

FDA Response
No, we do not agree. A minimum of 12 months of stability data is required at the time of NDA filing. Further, all product quality attributes need to have established acceptance criteria.

Meeting Discussion
This question was not discussed.

Question 11
At the time of NDA submission Teva will include (b) (4) months of stability for leachables. Does the Agency agree that the NDA may be updated no later than (b) (4) months into the review period with additional stability data (12 months)?

FDA Response
No, we do not agree. Refer to our response to Question 10.

Meeting Discussion
This question was not discussed.

Question 12
Is the proposed strategy for routine control of extractables and leachables acceptable?

FDA Response
Your approach is reasonable.

Meeting Discussion
This question was not discussed.

Question 13
(b) (4)

FDA Response
We do not agree. At least three months of accelerated and long term stability data is required to qualify a second manufacturing facility at the time of NDA filing. In addition, provide a commitment to complete the full stability study.

Meeting Discussion
This question was not discussed.

Additional CMC Comment
Clarify if in the case of breath actuation failure, the BDP BAI can be opened and actuated manually as a traditional press and breathe MDI. If such fallback mechanism is intended for the product, corresponding directions should be included in the prescribing information.

CLINICAL PHARMACOLOGY

Question 14
During the above referenced PIND meeting, the Food and Drug Administration (FDA) stated that, while PK BE between the BDP BAI and the QVAR MDI was not required under the 505(b)(2) application, it is desirable. FDA stated that they would review the data if BE is not demonstrated and that a (b) (4) *difference may not matter.*

In the BDB-AS-101 study, PK BE was demonstrated for maximum plasma concentration (C_{max}), area under the plasma concentration curve from 0 until the last time measured (AUC_{0-t}) and area under the plasma concentration curve from 0 until infinity ($AUC_{0-\infty}$) for the active metabolite beclomethasone17-monopropionate (17-BMP) which is the primary active moiety for

the product. Does the agency agree that these data are sufficient to demonstrate that the systemic exposure of the 2 products is equivalent?

FDA Response
Based on the data presented in this meeting package, it is reasonable to conclude that the systemic exposures of the major primary active metabolite, 17-BMP, from the two products are comparable. In addition, the clinical relevance of increased exposure of the beclomethasone propionate, when delivered through BDP BAI, will be a review issue.

Meeting Discussion
This question was not discussed.

Question 15
In study BDB-AS-101, PK BE was not demonstrated for C_{max} or AUC_{0-t} for beclomethasone dipropionate. However, Teva believes the results for the primary active moiety (17-BMP) and for the parent compound demonstrate that overall exposure between products is comparable. Does the agency agree that the PK results for beclomethasone dipropionate and 17-BMP support Teva's interpretation?

FDA Response
We agree that based on the data presented, it is reasonable to conclude that overall systemic exposures between two products are comparable. However, the clinical relevance of increased exposure of the beclomethasone propionate, when delivered through BDP BAI, will be a review issue.

Meeting Discussion
This question was not discussed.

Question 16
Does the agency agree that the PK study results demonstrate comparable systemic absorption and are adequate to extrapolate the results from the MDI inhalation aerosol (QVAR MDI) program (NDA 20-911, NDA 20-911/S5, NDA 20-911/S8) as supportive data for the proposed BAI clinical program?

FDA Response
In general, your approach seems reasonable. However, final assessment on the adequacy of the PK study results to support BAI clinical program will be a review issue.

Meeting Discussion
This question was not discussed.

Question 17
Does the agency agree that dose proportionality and relative bioavailability are demonstrated between the BDP BAI 40 mcg, BDP BAI 80 mcg, and the QVAR MDI 80 mcg products?

FDA Response
In general your approach seems reasonable. However, the adequacy of dose proportionality and relative bioavailability study is a review issue, and hence we cannot comment on it at this stage.

Meeting Discussion
This question was not discussed.

CLINICAL

Question 18
Teva plans to collect at least 100 normally functioning, active investigational product BAIs from each strength (40 mcg and 80 mcg) for end of life testing and examination from the BDB-AS-301 and BDB-AS-304 studies. Teva also plans to collect all malfunctioning BAI devices from all 3 clinical studies for further investigation.

Does FDA agree that collection of the active BAI devices from the 2 mentioned studies will be sufficient for the overall program and that no collection from the BDB-AS-302 pediatric study for routine end of life testing is required?

FDA Response
Your proposal to collect 100 normally functioning, active investigational product BAIs from each strength in both of the phase 3 adolescent and adult studies (BDB-AS-301 and BDB-AS-304) is acceptable. We also agree with your plan to collect all malfunctioning BAI devices from all 3 studies (including the pediatric study BDB-AS-302).

Additional Clinical Comments
We note that in Study BDB-AS-302 you plan to enroll subjects (b) (4) 11 years of age. We recommend including children down to age 4 in Study BDB-AS-302 as literature supports consistent inspiratory flow rates in children ≥ 4 years of age which would be adequate for your proposed product. Moreover, corticosteroid MDI press and breath inhalers, which require more coordination, are approved down to age 4 for the treatment of asthma.

Teva's Comment
We have the following comment regarding the statements in your response:

In additional clinical comments above, the FDA recommended that Teva include patients as young as age 4 in the BDB-AS-302 study. The protocol currently includes patients as young as age (b) (4) however, we have experienced significant difficulty in enrolling patients in this age group in large part due to the difficulty these young patients have performing adequate spirometry and meeting spirometry-related entry criteria. As an example, the current screen fail rate in patients age (b) (4) is over 80%. Based on these challenges and as we anticipate that patients age 4 would have even more difficulty performing adequate spirometry, we propose that the protocol be amended to include patients as young as age 4, but exclude the spirometry procedures for patients 5 years and younger. This is consistent with other programs of similar design that have included children in this age range. These patients would be required to meet all other inclusion

criteria for randomization and safety and efficacy evaluation would be based on assessment of non-spirometry endpoints.

Is this approach acceptable?

Meeting Discussion

FDA agreed with Teva's proposal but recommended adding other inclusion and efficacy criteria such as peak flow rates. While FDA encouraged the inclusion of patients even if they could not perform spirometry, FDA advised that the Sponsor should attempt to obtain spirometry data in the younger patients, and use the data from those patients who could perform spirometric measures in the efficacy analysis. Those 4 (b) (4) year olds who are unable to perform spirometry would still be important to inform safety.

STATISTICS

Question 19

As originally agreed with FDA in the PIND meeting held 28 September 2012 (see Appendix A for the meeting minutes) and the subsequent Type C meeting held 29 August 2013 (Appendix B) the primary efficacy measure for the ongoing BDB-AS-301 and BDB-AS-304 studies is the change from baseline in trough morning (pre-dose and pre rescue bronchodilator) forced expiratory volume in 1 second (FEV_1) over the 12-week treatment period. The BDB-AS-302 pediatric study primary efficacy measure is the change from baseline in trough morning (pre-dose and pre-rescue bronchodilator) percent predicted FEV_1 over the 12-week treatment period. In each study, the primary efficacy measure will be evaluated through estimation of the time averaged difference in FEV_1 between treatment groups over the 12 weeks utilizing mixed-effects model for repeated measures (MMRM) methodology.

In communications from FDA on 6 March 2014 (Appendix C) and 15 April 2014 (Appendix D) Teva was asked to change the primary efficacy measure from time-averaged change in FEV_1 to a landmark endpoint, such as change from baseline in FEV_1 at week 12. Further, FDA indicated change from baseline in FEV_1 over the 12 week treatment period may be considered a secondary endpoint.

Teva has considered the feedback provided during these and subsequent interactions and believes the original agreed primary efficacy measure and analysis methodology are the most appropriate for the previously agreed study design in this ongoing program that is nearing completion. Mindful of FDA interest in assessing other outcome measures and methodologies, Teva would consider evaluation of appropriate alternate endpoints and methodologies as secondary and exploratory supportive analyses.

Does the Agency agree with retaining the primary endpoints and analysis methodology in this near completed program as agreed to at the PIND meeting and the subsequent Type C meeting?

FDA Response

We stand by our suggestions for the landmark primary endpoint as stated in the April 15, 2014 teleconference. Products associated with initial large differences between treatment and placebo

but small (if any) difference from placebo at the end of the double blind treatment period are clinically undesirable so that the landmark analysis is preferred to an analysis of the average over time. We recommend that outcome measures for patients who discontinue study treatment early continue to be collected and be used in your primary analysis. Alternatively, a cumulative responder analysis considering patients who discontinue study medication early as failures would be appropriate as a primary analysis. Although defining the primary analysis is at your discretion, we will consider the landmark analysis using retrieved dropout data and/or the cumulative responder analysis for decision making. Differences between these analyses and the analysis you are proposing will be a review issue.

Teva's Comment

We have three questions regarding the following three statements in your response:

1. ***"Although defining the primary analysis is at your discretion...":*** *The primary analysis was specified a priori in the protocol based on a time-averaged measure. Our understanding is that FDA does not like sponsors redefining the primary analysis late in the conduct of the study or when the study is concluded. As such, Teva seeks further clarification as to where this discretion lies.*

2. ***"we will consider the landmark analysis using retrieved dropout data...":*** *As both studies are near complete, and retrieved dropout data have not been collected (as per protocol), we do not have the retrieved dropout data available to feasibly conduct the proposed approach. As described in the briefing materials, since this drug is a substitute for the standard treatment, not an add-on, and the controls remaining in the study are a biased subset of the randomized controls, Teva seeks further clarification on the clinical rationale and justification for this type of landmark analysis in placebo-controlled trials of this design and how FDA would interpret the results of this approach.*

3. ***"and/or the cumulative responder analysis for decision making":*** *This is also a post-hoc revision of the pre-specified primary analysis; our understanding is that the cumulative responder analysis is descriptive in nature and does not provide a single p-value but rather a range of answers according to the choice of cut-off. As such, Teva seeks further clarification on how the FDA would interpret the results of this approach.*

Meeting Discussion

Teva questioned the appropriateness of a change to the protocol at such a late stage. FDA replied that such a change has been under discussion for a long time, and we still consider it appropriate.

FDA clarified that the cumulative responder analysis is neither an analysis of completers only nor a responder analysis with a single cutoff. Rather, it is an analysis of responders at all possible cutoffs simultaneously, which amounts to an analysis of empirical cumulative distribution functions with dropouts assigned bad scores.

Teva noted a possible decreased efficiency of landmark analysis based only on the final observation rather than some analysis based on an average of observations. FDA

encouraged the use of efficient methods as long as dropouts were not assigned good outcomes based on good observations before dropout.

3. ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its

October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also

include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4. ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

5. ACTION ITEMS
There were no action items.

6. ATTACHMENTS AND HANDOUTS
There were no attachments or handouts for the meeting minutes.

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

/s/

PHUONG N TON
10/23/2014