

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205636Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205636

SUPPL # 0

HFD # 570

Trade Name: ProAir RespiClick

Generic Name: Albuterol sulfate

Applicant Name: Teva Pharmaceuticals

Approval Date, If Known: May 06, 2015

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)

c) 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:

d) Did the applicant request exclusivity?

YES NO

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

(b) (4)

e) 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?

No

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# 020503 Proventil HFA

NDA# 021457 ProAir HFA

NDA# 020983 Ventolin HFA

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:

ABS-AS-301, ABS-AS-304, ABS-AS-302, ABS-AS-307 and ABS-AS-308

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: Study ABS-AS-301	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2: Study ABS-AS-304	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3: Study ABS-AS-302	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4: Study ABS-AS-307	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #5: Study ABS-AS-308	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #6:	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #7:	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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: Study ABS-AS-301	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2: Study ABS-AS-304	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3: Study ABS-AS-302	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4: Study ABS-AS-307	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #5: Study ABS-AS-308	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #6:	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #7:	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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"):

Investigation #1: Study ABS-AS-301

Investigation #2: Study ABS-AS-304

Investigation #3: Study ABS-AS-302

Investigation #4: Study ABS-AS-307

Investigation #5: Study ABS-AS-308

Investigation #6:

Investigation #7:

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: Study ABS-AS-301

IND # 104532 YES ! NO
! Explain:

Investigation #2: Study ABS-AS-304

IND # YES ! NO
! Explain:

Investigation #3: Study ABS-AS-302

IND # 104532 YES ! NO
! Explain:

Investigation #4: Study ABS-AS-307

IND # 104532 YES ! NO
! Explain:

Investigation #5: Study ABS-AS-308

IND # 104532 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:

Investigation #2
!
! YES
! NO
! 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: Nikolay Nikolov, M.D.
Title: Clinical Team Leader
Date: March 03, 2015

Name of Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.
Title: Division Director
Date: March 18, 2015

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/

LEILA P HANN
03/31/2015

BADRUL A CHOWDHURY
03/31/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205636 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: ProAir RespiClick Established/Proper Name: albuterol sulfate MDPI Dosage Form: powder for inhalation		Applicant: Teva Branded Pharmaceuticals R&D, Inc. Agent for Applicant (if applicable):
RPM: Leila P. Hann		Division: DPARP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>May 06, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None TA 03/05/2015
❖ 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 _____		<input type="checkbox"/> 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, (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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 3
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> 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	X No <input type="checkbox"/> 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.	X Verified <input type="checkbox"/> 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 (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval 03/31/2015 Tentative Approval 03/05/2015
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included 03/23/2015
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	X Included 05/05/2014
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included 03/23/2015
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	X Included 05/05/2014
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	X Included 03/10/2014
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	07/18/2014 07/16/2014
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None 07/07/2014 DMEPA: <input type="checkbox"/> None 01/16/2015; 12/10/2014 DMPP/PLT (DRISK): <input type="checkbox"/> None 02/24/2015 OPDP: <input type="checkbox"/> None 02/25/2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	06/30/2014; 03/30/2015
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 03/18/2015
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> 03/31/2015
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes X No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>01/07/2015</u> If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	03/25/2015; 03/20/2015; 03/10/2015; 03/04/2015; 02/26/2015; 02/23/2015; 02/20/2015; 02/10/2015; 02/04/2015; 12/18/2014; 11/03/2014; 07/08/2014; 06/09/2014; 06/03/2014; 05/15/2014; 05/12/2014
❖ 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 <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 11/19/2013 <input type="checkbox"/> No mtg 10/05/2010 <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None 03/31/2015; 03/04/2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None 02/11/2015
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 3
Clinical	
❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review 01/28/2015; 06/04/2014 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	02/23/2015

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	X N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 01/15/2015; 06/16/2014
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 01/27/2015; 06/09/2014
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 02/04/2015
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 01/27/2015; 06/18/2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 01/28/2015; 01/27/2015; 06/23/2014; 06/13/2014; 06/05/2014
❖ Microbiology Reviews X NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		<input type="checkbox"/> Not needed 03/31/2015; 05/29/2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		01/27/2015
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>		Date completed: 02/20/2015 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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/s/

LEILA P HANN
03/31/2015



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

FACSIMILE TRANSMITTAL SHEET

DATE: March 25, 2015

To: William Kiddell Associate Director, Regulatory Affairs	From: Leila P. Hann
Company: Teva Branded Pharmaceutical Products R. &D., Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 305-575-6339	Fax number: 301-796-9728
Secure Email: William.Kiddell@tevapharm.com	Phone number: 301-796-3367

Subject: NDA 205636 ProAir RespiClick Information Request

Total no. of pages including cover: 3

Comments: PREA Post Marketing Requirements

Document to be mailed: YES xNO

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We refer to original NDA 205636 for ProAir RespiClick dated March 06, 2015. We request confirmation of your agreement to conduct the following studies and completion of milestone timelines. Provide updated information for milestone timelines that have been met.

PREA Postmarketing requirements (PMR)

PMR #1: To conduct a study to assess the pharmacokinetics of ProAir RespiClick in pediatric asthma patients between the ages 4 to 11 years.

PMR Scheduled milestones:

Final Protocol Submission:	05/09/2014
Trial Completion:	02/28/2015
Final Report Submission:	09/30/2015

PMR #2: To conduct a study to assess the efficacy and safety of two dose levels of ProAir RespiClick in pediatric asthma patients between the ages 4 to 11 years.

PMR Scheduled milestones:

Final Protocol Submission:	05/09/2014
Trial Completion:	02/28/2015
Final Report Submission:	09/30/2015

PMR #3: To conduct a study to assess the chronic-dose efficacy and safety of ProAir RespiClick in pediatric asthma patients between the ages 4 to 11 years.

PMR Scheduled milestones:

Final Protocol Submission:	05/09/2014
Trial Completion:	02/28/2015
Final Report Submission:	09/30/2015

Please provide a response to the requests by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by COB March 26, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Senior Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ March 25, 2015

Initialed by: S. Barnes/ March 25, 2015
S. Seymour/ March 25, 2015
N. Nikolov/ March 25, 2015

Finalized: L. Hann/ March 25, 2015

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/s/

LEILA P HANN
03/25/2015



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FACSIMILE TRANSMITTAL SHEET

DATE: March 20, 2015

To: William Kiddell Associate Director, Respiratory	From: Leila P. Hann, Senior Regulatory Project Manager
Company: Teva Research and Development	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Telephone number: 305-575-6336	Fax number: 301-796-9728
Secure Email: William.kiddell@tevapharm.com	Phone number: 301-796-3367
Subject: NDA 205636 (ProAir RespiClick) Information Request	

Total no. of pages including cover: 21

Comments:

Document to be mailed: YES xNO

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Your NDA 205636 submitted on March 06, 2015 is currently under review. We have the following comments regarding the March 10, 2015 submission in the attached label. These are our current edits and there may be additional comments.

Submit revised draft labeling incorporating the attached changes.

In order to facilitate the review of your NDA submission, provide the requested information no later than 2:00 PM, March 24, 2015. If you have any questions, please contact Leila P. Hann, Senior Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ March 18, 2015
Cleared by: N. Nikolov/ March 20, 2015
C. Bertha/ March 19, 2015
Y. Hu/ March 19, 2015
Y. Ren/ March 18, 2015
S. Barnes/ March 20, 2015
Finalized by: L. Hann/ March 20, 2015

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/s/

LEILA P HANN
03/20/2015



NDA 205636

**ACKNOWLEDGE -
CLASS 1 COMPLETE RESPONSE**

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

Attention: William Kiddell,
Associate Director, Respiratory

Dear Mr. Kiddell:

We acknowledge receipt on March 06, 2015, of your March 06, 2015, resubmission to your supplemental new drug application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for ProAir RespiClick (albuterol sulfate) powder for inhalation, 90mcg.

The resubmission contains additional patent information that you submitted in response to our March 05, 2015 tentative approval letter.

We consider this resubmission a complete, class 1 response to our action letter. Therefore, the user fee goal date is May 06, 2015.

If you have any questions, call me at (301) 796-3367.

Sincerely,

{See appended electronic signature page}

Leila P. Hann
Senior Regulatory 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/

LEILA P HANN
03/10/2015



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

FACSIMILE TRANSMITTAL SHEET

DATE: March 04, 2015

To: William Kiddell Associate Director, Respiratory	From: Leila P. Hann, Senior Regulatory Project Manager
Company: Teva Research and Development	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Telephone number: 305-575-6336	Fax number: 301-796-9728
Secure Email: William.kiddell@tevapharm.com	Phone number: 301-796-3367
Subject: NDA 205636 (ProAir RespiClick) Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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Your NDA 205636 submitted on May 05, 2014 is currently under review. We have the following comments regarding the Prescribing Information, Patient Information, and Carton. There may be additional comments.

Prescribing Information:

For Section 5.1 of the PI, revise as follows:

5.1 Paradoxical Bronchospasm

PROAIR RESPICLICK (b) (4) can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, PROAIR RESPICLICK should be discontinued immediately and alternative therapy instituted.

Carton Label:

Revise the phrase “**IMPORTANT INFORMATION**” to read “**IMPORTANT RISK INFORMATION**” or “**IMPORTANT SAFETY INFORMATION**”

Patient Information:

The most common side effects of PROAIR RESPICLICK include:

- back pain
- body aches and pain
- upset stomach (b) (4)

Submit revised draft labeling incorporating the above changes.

In order to facilitate the review of your NDA submission, provide the requested information no later than March 04, 2015. If you have any questions, please contact Leila P. Hann, Senior Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ March 04, 2015
Cleared by: N. Nikolov/ March 04, 2015
S. Barnes/ March 04, 2015
Finalized by: L. Hann/ March 04, 2015

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/s/

LEILA P HANN
03/04/2015



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FACSIMILE TRANSMITTAL SHEET

DATE: February 26, 2015

To: Steve Viti, Ph.D., M.B.A. Senior Directory, Regulatory Affairs	From: Leila P. Hann, Senior Regulatory Project Manager
Company: Teva Research and Development	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Telephone number: 305-575-6336	Fax number: 301-796-9728
Secure Email: steve.viti@tevapharm.com	Phone number: 301-796-3367

Subject: NDA 205636 (ProAir RespiClick) Information Request

Total no. of pages including cover: 13

Comments:

Document to be mailed: YES xNO

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Your NDA 205636 submitted on May 05, 2014 is currently under review. We have the following comment regarding the Patient Package Insert and Information for Use. There may be additional comments.

Submit revised draft labeling incorporating changes in the attached marked up labels.

In order to facilitate the review of your NDA submission, provide the requested information no later than COB, March 03, 2015. If you have any questions, please contact Leila P. Hann, Senior Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ February 26, 2015
Cleared by: N. Nikolov/ February 26, 2015
S. Barnes/ February 26, 2015
Finalized by: L. Hann/ February 26, 2015

10 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

LEILA P HANN
02/26/2015



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 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 23, 2015

To: Steve Viti, Ph.D., M.B.A. Senior Directory, Regulatory Affairs	From: Leila P. Hann, Senior Regulatory Project Manager
Company: Teva Research and Development	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Telephone number: 305-575-6336	Fax number: 301-796-9728
Secure Email: steve.viti@tevapharm.com	Phone number: 301-796-3367

Subject: NDA 205636 (ProAir RespiClick) Information Request

Total no. of pages including cover: 18

Comments:

Document to be mailed: YES xNO

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Your NDA 205636 submitted on May 05, 2014 is currently under review. We have the following comments regarding the February 11, 2015 submission in the attached label. There may be additional comments.

In order to facilitate the review of your NDA submission, provide the requested information no later than COB, February 27, 2015. If you have any questions, please contact Leila P. Hann, Senior Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ February 23, 2015
Cleared by: S. Barnes/ February 23, 2015
Finalized by: L. Hann/ February 23, 2015

13 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

LEILA P HANN
02/23/2015



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 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 20, 2015

To: William Kiddell Associate Director, Regulatory Affairs	From: Leila P. Hann
Company: Teva Branded Pharmaceutical Products R. &D., Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 305-575-6339	Fax number: 301-796-9728
Secure Email: William.Kiddell@tevapharm.com	Phone number: 301-796-3367
Subject: NDA 205636 Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your NDA 205636 submitted May 05, 2014, is currently under review and we have the following comments:

A full approval action is not be possible on the PDUFA date of March 5, 2015 as the 45 day period in which the patent owner has to file suit will end at midnight on March 5, 2015.

You may obtain a pathway to full approval on the PDUFA date by one of the following two options:

1. Waiver of opportunity to file legal action within 45 days of receipt of notice: The patent owner or NDA holder (if the NDA holder is an exclusive patent licensee) may waive the opportunity to file a legal action for patent infringement within the 45-day period following receipt of notice. However, FDA will only accept a waiver in the form described in 21 CFR 314.107(f)(3), so you should request that each patent owner/NDA holder provide a letter containing the specific waiver language set forth in this regulation.
2. Licensing agreement: If Teva Branded obtains a license to the '321 and '745 patent and the patent owner "consents to an immediate effective date of approval of the 505(b)(2) application," then you may submit a "written statement from the patent owner that it has a licensing agreement with the applicant and that the patent owner consents to an immediate effective approval date." (21 CFR 314.50(i)(3)).

Please provide a response to the requests by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by Noon on Wednesday, February 25, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Senior Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ February 20, 2015
Cleared by: S. Stradley/ February 20, 2015
S. Barnes/ February 20, 2015
Finalized by: L. Hann/ February 20, 2015

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/s/

LEILA P HANN
02/20/2015



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 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 10, 2015

To: Steve Viti, Ph.D., M.B.A. Senior Directory, Regulatory Affairs	From: Leila P. Hann, Senior Regulatory Project Manager
Company: Teva Research and Development	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Telephone number: 305-575-6336	Fax number: 301-796-9728
Secure Email: steve.viti@tevapharm.com	Phone number: 301-796-3367

Subject: NDA 205636 (ProAir RespiClick) Information Request

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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Your NDA 205636 submitted on May 05, 2014 is currently under review. We have the following comments regarding carton and container labeling. These are the preliminary edits and there may be additional comments.

All Label and Labeling

1. Utilize the same font color of the name 'ProAir' in the name 'RespiClick'. As presented the 'RespiClick' (b) (4) and is not as prominent as 'ProAir' which may cause potential confusion between this product and the currently marketed ProAir HFA if the 'RespiClick' is overlooked.

Carton and Container Labeling

2. Relocate the strength from the bottom of the labeling to after the dosage form so that it is easily recognized: see example below
ProAir RespiClick
(Albuterol Sulfate) Inhalation Powder
(b) (4)
3. Relocate the statement 'With Dose Counter' to below the graphic to allow for the placement of the strength statement.
4. Consider utilizing a different color (other than red) to avoid potential confusion between this product and the currently marketed ProAir HFA which also utilizes a red color.
5. The strength of the product should be expressed as the metered dose. In addition, since the established name of your product is albuterol sulfate, the strength should also correspond to the metered dose of the salt. Revise the strength of the product from (b) (4) (b) (4) to "117 mcg" (b) (4) dose.
6. Revise (b) (4) to "CONTENTS: Each metered dose contains 117 mcg of albuterol sulfate and delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) with lactose from the mouthpiece"
7. Include Lot Number and Expiration Date in the labels.

In order to facilitate the review of your NDA submission, provide the requested information no later than COB, February 17, 2015. If you have any questions, please contact Leila P. Hann, Senior Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ February 09, 2015
Cleared by: S. Barnes/ February 10, 2015
Finalized by: L. Hann/ February 10, 2015

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/s/

LEILA P HANN
02/10/2015



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FACSIMILE TRANSMITTAL SHEET

DATE: February 04, 2015

To: Steve Viti, Ph.D., M.B.A. Senior Directory, Regulatory Affairs	From: Leila P. Hann, Senior Regulatory Project Manager
Company: Teva Research and Development	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Telephone number: 305-575-6336	Fax number: 301-796-9728
Secure Email: steve.viti@tevapharm.com	Phone number: 301-796-3367

Subject: NDA 205636 (ProAir RespiClick) Information Request

Total no. of pages including cover: 18

Comments:

Document to be mailed: YES xNO

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Your NDA 205636 submitted on May 05, 2014 is currently under review and we have the following labeling comments. These are the preliminary edits and there may be additional comments. Submit revised draft labeling incorporating changes in the attached marked up label.

FDA edits were made as tracked changes to the clean version of your proposed label. Any additional proposed changes you may have can be made in a similar fashion by using a clean version of the attached PI and edit using tracked changes.

In order to facilitate the review of your NDA submission, provide the requested information no later than COB, February 11, 2015. If you have any questions, please contact Leila P. Hann, Senior Regulatory Project Manager, at 301-796-3367.

Drafted by: L. Hann/ February 03, 2015
Cleared by: S. Barnes/ February 04, 2015
Finalized by: N. Ton/ February 04, 2015

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/s/

PHUONG N TON
02/04/2015



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FACSIMILE TRANSMITTAL SHEET

DATE: December 18, 2014

To: William Kiddell Associate Director, Regulatory Affairs	From: Leila P. Hann
Company: Teva Branded Pharmaceutical Products R. &D., Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 305-575-6339	Fax number: 301-796-9728
Secure Email: William.Kiddell@tevapharm.com	Phone number: 301-796-3367
Subject: NDA 205636 Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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Your NDA 205636 submitted May 05, 2014, is currently under review and we have the following request for information:

1. Revise the drug product specification as follows:

- a. Tighten the acceptance criterion for Net Content (Fill) Weight to (b) (4) g, which is the fill weight limits determined in Section P.2.2.2 of the NDA.
- b. Tighten the acceptance criterion for Assay (Total Drug Content per inhaler) to (b) (4) mg of albuterol base/inhaler.
- c. Revise the acceptance criteria for the APSD as highlighted below.
For n=5 inhalers, perform determinations on each inhaler at beginning and end. Report mass deposition **for each individual determination** in 4 groups:
Group 1 (MP/IP, Pre-Separator) (b) (4) μg
Group 2 (Stage 1, 2) (b) (4) μg
Group 3 (Stage 3, 4, & 5) (b) (4) μg
Group 4 (Stage 6, 7 & MOC) (b) (4) μg
The mass balance is within (b) (4) % of label claim emitted dose for each individual test.
- d. Clarify what the Cat. Nos. mean in the acceptance criteria for the Dose Counter Reading. Propose a single set of acceptance criteria for the Dose Counter Reading.

2. Provide justification for the use of (b) (4) actuations in each APSD determination for the drug product. The number of actuations needed to determine particle size distribution by multistage cascade impactor should be kept to the minimum justified by the sensitivity of the analytical method used to quantitate the deposited drug substance. The amount of drug substance deposited on the critical stages of the cascade impactor should be sufficient for reliable assay, but not so excessive as to bias the results by masking individual actuation variation.

Please provide a response to the requests by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by Noon on Tuesday, January 06, 2015. Your response must also be submitted formally to the NDA shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ December 18, 2014
Cleared by: Y. Hu/ December 18, 2014
J. Pinto/ December 18, 2014
S. Barnes/ December 18, 2014
Finalized by: L. Hann/ December 18, 2014

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/s/

LEILA P HANN
12/18/2014



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 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 03, 2014

To: William Kiddell Associate Director, Regulatory Affairs	From: Leila P. Hann
Company: Teva Branded Pharmaceutical Products R. &D., Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 305-575-6339	Fax number: 301-796-9728
Secure Email: William.Kiddell@tevapharm.com	Phone number: 301-796-3367
Subject: NDA 205636 Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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Your NDA 205636 submitted May 05, 2014, is currently under review and we have the following request for information:

Note that the FDA issued a new Clinical Pharmacology Labeling Guidance in August 2014: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm109739.pdf>

The organization of the Clinical Pharmacology section of your label should be modified to reflect the new guidance. Re-organize the structure in Clinical Pharmacology sections 12.2 and 12.3 in your proposed label to reflect the current format.

Submit the revised labeling as soon as possible so that we can continue our review. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ November 03, 2014
Cleared by: Y. Ren/ October 31, 2014
S. Brar/ October 31, 2014
S. Barnes/ November 03, 2014
Finalized by: L. Hann/ November 03, 2014

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/s/

LEILA P HANN
11/03/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205636

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Molly Shea, PhD.
Director, Regulatory Affairs

Dear Dr. Shea:

Please refer to your New Drug Application (NDA) dated and received May 5, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Albuterol Sulfate Inhalation Powder, 90 mcg per actuation.

We also refer to your correspondence dated and received May 5, 2014, requesting review of your proposed proprietary name, ProAir RespiClick.

We have completed our review of the proposed proprietary name, ProAir RespiClick, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your May 5, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Leila Hann, Regulatory Project Manager, in the Office of New Drugs at (301) 796-3367.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
07/18/2014



NDA 205636

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

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

Attention: Molly E. Shea, Ph.D.
Director, Regulatory Affairs

Dear Dr. Shea:

Please refer to your New Drug Application (NDA) dated May 05, 2014, received May 05, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ProAir RespiClick, (albuterol sulfate) powder for inhalation 90 mcg.

We also refer to your amendment dated June 12, 2014.

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 March 05, 2015

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 February 05, 2015.

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

CMC

1. Provide data to support the label claim strength of the drug product for the label/labeling. We remind you of our communication dated May 6, 2010, where we had informed you

that the strength of the product should correspond to the metered dose, (b) (4)

We are providing the above comments to give you preliminary notice of potential review issues. 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 these issues during this review cycle, we may not consider your response before we take an action on your application.

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](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

1. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
2. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.
3. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.
4. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by July 28, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests 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.

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

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, 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.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Leila P. Hann, Regulatory Project Manager, at (301) 796-3367.

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

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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/s/

BADRUL A CHOWDHURY
07/08/2014



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 09, 2014

To: Molly E. Shea, Ph.D. Director, Regulatory Affairs	From: Leila P. Hann
Company: Teva Branded Pharmaceutical Products R. &D., Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 305-575-6339	Fax number: 301-796-9728
Secure Email: Molly.Shea@tevapharm.com	Phone number: 301-796-3367
Subject: NDA 205636 Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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Your NDA 205636 submitted May 05, 2014, is currently under review and we have the following request for information:

1. Provide the programs and macros you used to analyze all efficacy and pharmacodynamic endpoints in dose accumulation study ABS-AS-101 and all efficacy endpoints in dose ranging study ABS-AS-201. For study ABS-AS-201, be sure to include programs and macros for analysis of ProAir HFA as well as for your proposed MDPI product.

Provide responses to this information request by 5:00 pm, EST on Monday June 23, 2014 by email at Leila.Hann@FDA.HHS.GOV. A formal submission to the NDA should be made shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ June 09, 2014
Cleared by: R. Abugov/ June 06, 2014
D. Petullo/ June 06, 2014
Y. Ren/ June 06, 2014
S. Brar/ June 06, 2014
S. Barnes/ June 09, 2014
Finalized by: L. Hann/ June 09, 2014

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/s/

LEILA P HANN
06/09/2014



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 03, 2014

To: Molly E. Shea, Ph.D. Director, Regulatory Affairs	From: Leila P. Hann
Company: Teva Branded Pharmaceutical Products R. &D., Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 305-575-6339	Fax number: 301-796-9728
Secure Email: Molly.Shea@tevapharm.com	Phone number: 301-796-3367
Subject: NDA 205636 (albuterol) Information Request	

**Total no. of pages including
cover:** 3

Comments:

Document to be mailed: YES xNO

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Your NDA 205636 submitted May 05, 2014, is currently under review and we have the following request for information:

Provide a letter of authorization (LoA) to allow our review of a Drug Master File from the manufacturer of the (b) (4) device (b) (4) that contains all of the pertinent CMC information. Alternately, amend the NDA to include this information (e.g., description of manufacturing processes including materials and manufacturing additives, acceptance testing of incoming materials, engineering drawings with dimensions and tolerances for device components and subassemblies, other specification tests and acceptance criteria related to device performance, cGMP status, etc.). The absence of this information may be considered to be a filing issue.

Provide responses to this information request by 5:00 pm, EST on Tuesday June 10, 2014 by email at Leila.Hann@FDA.HHS.GOV. A formal submission to the NDA should be made shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ June 03, 2014
Cleared by: C. Bertha/ June 03, 2014
E. Duffy/ June 03, 2014
S. Barnes/ June 03, 2014
Finalized by: L. Hann/ June 03, 2014

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/s/

LEILA P HANN
06/03/2014



NDA 205636

NDA ACKNOWLEDGMENT

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

Attention: Molly E. Shea, Ph.D.
Director, Regulatory Affairs

Dear Dr. Shea:

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: ProAir RespiClick, (albuterol) multi-dose powder inhaler at 90 µg

Date of Application: May 05, 2014

Date of Receipt: May 05, 2014

Our Reference Number: NDA 205636

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 July 04, 2014, 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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 (301) 796-3367.

Sincerely,

{See appended electronic signature page}

Leila P. Hann
Regulatory 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/

LEILA P HANN
05/15/2014



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 12, 2014

To: Molly E. Shea, Ph.D. Director, Regulatory Affairs	From: Leila P. Hann
Company: Teva Branded Pharmaceutical Products R. &D., Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 305-575-6339	Fax number: 301-796-9728
Secure Email: Molly.Shea@tevapharm.com	Phone number: 301-796-3367
Subject: NDA 205636 Information Request	

**Total no. of pages including
cover:** 3

Comments:

Document to be mailed: YES xNO

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Your NDA 205636 submitted May 05, 2014, is currently under review and we have the following request for information:

1. Provide the programs and macros used to analyze the primary efficacy endpoints, secondary efficacy endpoints, and patient disposition for studies ABS-AS-301, ABS-AS-302, and ABS-AS-304.

Provide responses to this information request by 5:00 pm, EST on Tuesday May 26, 2014 by email at Leila.Hann@FDA.HHS.GOV. A formal submission to the NDA should be made shortly thereafter. If you have any questions, please contact Leila P. Hann, Regulatory Program Manager, at 301-796-3367.

Drafted by: L. Hann/ May 12, 2014
Cleared by: R. Abugov/ May 12, 2014
D. Petullo/ May 12, 2014
S. Barnes/ May 12, 2014
Finalized by: L. Hann/ May 12, 2014

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/s/

LEILA P HANN
05/12/2014



IND 104532

MEETING MINUTES

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

Attention: Terry Duffield
Sr. Manager, Teva Global Branded Products Regulatory Affairs

Dear Ms. Duffield:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for albuterol Dry Powder Inhaler (“albuterol Spiromax”).

We also refer to the teleconference between representatives of your firm and the FDA on November 19, 2013. The purpose of the meeting was to discuss proposed changes relating to the manufacturing of the product and to receive guidance regarding the NDA submission.

A copy of the official minutes of the teleconference 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) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Chung, R.Ph.
CDR, U.S. Public Health Service
Program Coordinator
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: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: November 19, 2013 3:00 – 4:00 P.M.
Meeting Location: Teleconference

Application Number: IND 104532
Product Name: albuterol Dry Powder Inhaler (“albuterol Spiromax”)
Indication: Asthma, exercise-induced bronchospasm (EIB)
Sponsor/Applicant Name: Teva Branded Pharmaceutical Products R&D, Inc. (Teva)

Meeting Chair: Badrul A. Chowdhury, Director
Meeting Recorder: Christine Chung, Regulatory Project Manager

FDA ATTENDEES:

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Lydia Gilbert-McClain, M.D., Deputy Director, DPARP
Janet Maynard, M.D., Acting Clinical Team Leader, DPARP
Peter Starke, M.D., Clinical Reviewer, DPARP
Marcie Wood, Ph.D., Supervisory Pharmacologist, DPARP
Nik Patel, Ph.D., Pharmacology/Toxicology Reviewer, DPARP
Christine Chung, R.Ph., Regulatory Project Manager, DPARP
Prasad Peri, Ph.D., Branch Chief, Division of New Drug Quality Assessment (DNDQA) Branch VIII
Craig Bertha, Ph.D., Acting CMC Lead, DNDQA III
Satjit Brar, Ph.D., Team Leader, Division of Clinical Pharmacology II (DCP II)
Joan Buenconsejo, Ph.D., Biometrics Team Leader, Division of Biometrics II (DBII)
Kiya Hamilton, Ph.D., Biometrics Reviewer, DBII
Lissa Owens, Pharm.D., Safety Evaluator, Division of Medication Error Prevention & Analysis (DMEPA)
Dipti Kalra, R.Ph., Safety Evaluator, Division of Pharmacovigilance I
QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

SPONSOR ATTENDEES:

Name	Title
Christopher O'Brien, MD, PhD	Vice President, Global Respiratory R&D
Herminia Taveras, PhD, MPH	Sr. Manager Clinical Research, Teva Global Respiratory R&D
Youyi Shu, PhD	Sr. Director, Global Biostatistics
Harald Iverson, PhD	Associate Director, Biostatistics, Teva Global Respiratory R&D
Julian Blair, PhD	Sr. Director, Pharmaceutical Development, Teva Global Respiratory R&D
David Simento	Director, Project Management, Global Respiratory R&D
Steve Viti, PhD, MBA	Sr. Director, Teva Global Regulatory Affairs, Respiratory
Molly E. Shea, PhD	Director, Teva Global Regulatory Affairs, Respiratory
Terry Duffield	Sr. Manager, Global Regulatory Affairs, Respiratory
(b) (4)	Consultant, Regulatory Affairs

BACKGROUND:

Teva is developing albuterol SPIROMAX, a multidose, dry-powder, breath-actuated inhaler for proposed use in asthma and EIB. They state that the phase 3 clinical program is nearly complete and requested a pre-NDA meeting to discuss proposed changes relating to the manufacturing of the product and questions regarding the NDA submission. The briefing package was received October 18, 2013.

After review of the meeting package, FDA provided meeting preliminary comments to the sponsor's questions via a letter on November 18, 2013.

Teva emailed specified areas for further discussion regarding FDA responses to Questions 3 & 4, 6, 8, and 14. Regarding Question 12, Teva stated that they will submit their proposal for a sensitivity analysis and method of imputation to the IND for review.

The content of the letter is printed below, with the sponsor's questions from the briefing package in *italics* and FDA's responses (meeting preliminary comments) in normal font. Teva's questions for additional discussion during the teleconference are also noted in normal font. Summary of meeting discussions, if any, are found in **bold normal font** following the specific area of discussion.

QUESTIONS AND PRELIMINARY RESPONSES

Chemistry, Manufacturing and Controls

Question 1: We will submit at least 12 months of stability on 3 exhibit batches of the final (b) (4) device and 24 months of stability on 3 exhibit batches of the (b) (4) device for a total of 6 batches from the primary process on the (b) (4). In addition, Teva intends to qualify an (b) (4) (b) (4) for manufacturing the Albuterol SPIROMAX product at full commercial scale. At the time of NDA submission, Teva will include 1 month of stability for 3 batches manufactured on the (b) (4). Does the Agency agree that the NDA may be updated no later than 4 months into the review period with additional stability data (3 and 6 months) so that this line may be approved for commercial manufacture at launch?

FDA response:

Assuming that both lines are at the commercial site, the stability data proposal is acceptable.

Question 2: If the FDA agrees with the critical and non-critical component justifications and the requirements of the Comparability Protocol, can all post-approval component (b) (4) changes for critical components be made through a Changes Being Effected Supplement and all non-critical component (b) (4) changes be made by annual report?

FDA response:

Assuming that the Comparability Protocol is acceptable, it is feasible that changes in (b) (4) may be submitted via the regulatory mechanisms proposed.

Question 3: Does the Agency agree that following the Comparability Protocol would allow for postapproval changes through a Changes Being Effected Supplement?

FDA response:

A Comparability Protocol could allow changes to manufacturing sites of device components to be submitted via *Changes Being Effected* supplements depending on the requirements to be met in the protocol.

Question 4: Teva proposes to include the Comparability Protocols in the Pharmaceutical Development section 3.2.P.2 of the eCTD structure. Does the Agency agree with this placement?

FDA response:

We agree.

Additional Comment

Because patients may use the albuterol inhalation powder drug product on an *as needed* basis, design your in use-studies (studies of product stored without protective packaging) to address such a usage scenario.

Teva's clarification request:

For the Comparability Protocols, the Agency has advised us to design our in-use studies to address product stored without protective packaging. Is the Agency suggesting that stability studies under the Comparability Protocol should only be performed in the unwrapped configuration and only at 30C/65%RH, in keeping with previously agreed stability studies for unprotected product?

Discussion:

FDA clarified that the 'Additional Comment' above was not intended to be related to the Comparability Protocol that was the subject of question 4.

Clinical (Including Pediatric Study Questions)

Question 5: Previously, Teva has submitted Principal Investigator CVs and medical licenses in the clinical report study appendices. Is it acceptable to the Agency if we omit the Principal Investigator CVs and medical licenses in Appendix 16.1.4 of the clinical study report appendices?

FDA response:

Your request is acceptable. However, provide references to the location of those documents, should they be needed.

Question 6: In reference to the January 2013 guidance cited, will it also be acceptable to omit from Appendix 16.1.4 of the Phase 3 study reports the names of the Sub-Investigators who participated at each study site?

FDA response:

We disagree. Provide a listing of all investigators and sub-investigators at every site, along with the appropriate financial documentation for each.

Teva's clarification request:

As advised, we agree to provide a complete list of investigators and sub-investigators for each site in Appendix 16.1.4 to each clinical study report. Could the Agency clarify their comment regarding Financial Disclosure, ie, can they confirm Financial Disclosure information is not required within the clinical study report appendices and is to be included in Module 1 only as lists attached to the appropriate FDA form(s)?

Discussion:

FDA responded that Financial Disclosure information may be included in Module 1 (as per *Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators*, dated 2/2013, found at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf>).

Question 7: Given the differences in formulation and delivery mechanism, Teva believes that PREA is applicable to Albuterol SPIROMAX. Does the Agency agree?

FDA response:

PREA will be triggered by the application, but it will be triggered because of the new dosage form, and not because of differences in the formulation and delivery mechanism. (The statement that serves as the basis of your question is incorrect.)

Question 8: At the time of NDA submission, Teva proposes to submit a pediatric waiver for patients 0 to 3 years of age. The basis of the waiver is section 505B(a)(4)(B) of the Act; studies of Albuterol SPIROMAX in this age group are impossible or highly impracticable due to the nature of the drug-device delivery. Therefore, the NDA will include a request for a partial waiver for study in infants and children 0 to 3 years of age in accordance with 21 CFR 314.55. Is this approach acceptable to the Agency?

FDA response:

In principle, your approach is acceptable. However, you will need to substantiate your reasoning for a waiver in the 0 through 3 year old age group by submitting information about the minimum flow rate required to appropriately use the Spiromax device, along with the expected flow rates for all pediatric age groups, including the age groups for which you are seeking a waiver. We also recommend that you support your position by providing data with regard to what happens to the delivered dose if a spacer is used with the Spiromax device.

Teva's clarification request:

For pediatric studies, Teva agrees to assess the minimum flow rate required to use the SPIROMAX device for the pediatric age group 4-11 years of age. We also will assess the feasibility of determining the minimum flow rate for the age group 0-3, for which we will seek a waiver. Teva requests clarification on why the Agency's is recommending that we provide data with regard to what happens to the delivered dose if a spacer is used with the SPIROMAX device, because we are not aware of any spacer that works /is intended to be used with a dry powder inhaler.

Discussion:

FDA responded that the albuterol SpiroMax in appearance looks very much like a DPI, and parents may try to use it with a spacer. FDA stated that although we conceptually agree that no spacer should be used with a DPI, it would be helpful to have in vitro data to support the labeling warning as such.

Teva asked even if data generated reflected otherwise, would it still be appropriate to label not to use with a spacer?

FDA responded that it is an open ended question at this time. It would be a review issue if the full dose is delivered with the spacer, however, they suspect that patients 0 to 3 years of age may not be able to generate the flow rate needed with a DPI. The in vitro data generated would be used to decide how strongly to word the warning. For example, if in vitro data show no drug comes when used with a spacer, then labeling language may say, "Do not use with spacer because no drug will be

delivered.” However, if some quantity of the drug comes with a spacer, then labeling may be silent on use with spacers, as it is with MDI’s.

Question 9: The adult and adolescent data are currently planned to be submitted as the primary NDA submission followed by a supplemental NDA for the pediatric program. Teva proposes to submit a deferral request for pediatric studies for patients 4 to 11 years of age in the NDA because the adult program is almost finished and the pediatric program is still underway. The conduct of the Phase 1 pediatric pharmacokinetic study (ABS-AS-102) and the pediatric single-dose, dose-ranging study (ABS-AS-202) were initiated in accordance with the agreement during the EOP2 clinical meeting of October 5, 2010. Teva plans to request a pediatric program EOP2 meeting at a later date to discuss the planned pediatric program in detail. Is it acceptable to request the deferral for patients 4 to 11 years of age in the NDA?

FDA response:

Your request for a deferral is acceptable, and we acknowledge your initial Pediatric Study Plan submitted November 12, 2013. Refer to PREA REQUIREMENTS paragraphs below.

Statistics

Question 10: It is proposed that an integrated summary of efficacy (ISE) will be comprised of side-by-side presentation as well as combined data presentation from the replicate 12-week, double-blind, controlled studies ABS-AS-301 and ABS-AS-304. Does the Agency agree with the proposed ISE approach?

FDA response:

Yes, this appears reasonable.

Question 11: It is proposed that an integrated summary of safety (ISS) will include a pooled presentation of placebo-controlled data from Studies ABS-AS-301, ABS-AS-304, and the placebo-controlled 12-week portion of Study ABS-AS-307. Additional data from open label (fixed-dose) and long-term safety (taken as needed) program components will also be presented as supportive information for safety assessment, but will not be pooled. Overall exposure across the program will be tabulated. Does the Agency agree with the proposed ISS approach?

FDA response:

Yes, this appears reasonable.

Question 12: Based on the 2010 EOP2 meeting, a mixed-model repeated-measures analysis (MMRM) is proposed for the ABS-AS-301 and ABS-AS-304 studies. This model will be used to evaluate performance over the entire treatment period (ie, the average of the estimates at visits at which FEV1 was collected) as well as at each visit, and to make a comparison of the first and last visits. A comprehensive plan will be implemented to find the reason for each dropout. If there are dropouts that are determined to be potentially not missing at random (MAR), a multiple imputation procedure will be performed to assess the sensitivity of the analysis to the MAR assumption. Does the Agency agree with the approach?

FDA response:

In general, your plan on how to evaluate the primary endpoint and your plan to examine the impact of missing data are reasonable. However, in order for us to comment or to agree with your choice of sensitivity analysis, provide details about the proposed multiple imputation procedure.

Teva's clarification request:

We appreciate the Agency's willingness to comment on our choice of a sensitivity analysis and the method of multiple imputation. We would be able to provide an overview tomorrow before the teleconference. Would the Agency be able to comment during the teleconference, or should our detailed proposal be provided for review and comment at a later time?

Discussion:

In order to allow for FDA review and comment, Teva stated that they will submit their proposal for a sensitivity analysis and method of imputation to the IND.

Question 13: Teva proposes that if datasets are submitted in the NDA in accordance with CDISC standards, individual patient profiles are not necessary. Does the Agency agree?

FDA response:

This is acceptable. However, be aware that individual patient profiles should be available in a timely manner should they be requested during the review period.

Regulatory/Other

Question 14: Teva performed Human Factors testing in keeping with industry trends and other Teva Respiratory product development programs. This program followed the risk-based approach recommended by FDA in the 2011 draft guidance "Applying Human Factors and Usability Engineering to Optimize Device Design." Teva believes this testing meets the requirements needed to support the application with no additional assessment (eg, "label comprehension" study). Does the Agency agree that the described Phase 3 in-use studies and the Human Factors program are sufficient to support the application?

FDA response:

Your approach seems reasonable; however, it will be a review issues as we do not have enough information to assess the design of the study and the results. To fully evaluate the nature and the rationale for all of the iterative changes and mitigations that you have made to the device user interface and how it has been optimized for safe and effective use, provide a table that links the use-related risks, the use errors/failures that may result in harm (in particular overdose) and were observed in these formative studies, and the iterative changes and additional mitigations that have been implemented to address those errors and failures. Also submit the results of all your formative testing, and discuss how these studies inform product design and labeling (IFU) as well as the design of your final human factors summative/validation testing. Submit the validation study protocol and results for our evaluation.

Teva's clarification request:

We wish to clarify that the Human Factors data detailed in the Agency's response is to be provided to the Agency in the NDA, and not prior to submission of the NDA.

Discussion:

FDA agreed.

Question 15: Teva proposes to place the Human Factors information (Risk Assessment and reports) in Module 3.2.P.2.4 (Container Closure System). Does the Agency agree this is the appropriate placement in the eCTD structure of the NDA?

FDA response:

We agree.

FDA Nonclinical comment

For your NDA submission, monitor impurities and degradation products of all active ingredients and refer to ICH Guidance [ICH Q3A(R2) and ICH Q3B(R)] for possible qualification requirements. Impurities or degradants of active ingredients that are identified as structural alerts should be at or below acceptable qualification thresholds to support your NDA as described in the ICH M7 Draft Consensus Guideline, "*Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (Step 2 Version dated February 6, 2013)*".

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 (PSP) within 60 days of an End of Phase (EOP2) meeting. 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.

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 Pediatric and Maternal Health Staff 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. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements of Prescribing Information website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, 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. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

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 (used for primary stability, biobatches, clinical studies and proposed commercial) 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). Provide a statement that each facility is 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

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. 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 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 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 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)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>

4.	
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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.

ISSUES REQUIRING FURTHER DISCUSSION:

There were no issues requiring further discussion.

ATTACHMENTS:

None.

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

/s/

CHRISTINE H CHUNG
12/16/2013



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type B
Meeting Category: End of Phase 2
Meeting Date and Time: October 5, 2010; 1:30 P.M.-2:30 P.M.
Meeting Location: Teleconference
Application Number: IND 104,532
Product Name: Albuterol Spiromax
Received Briefing Package August 30, 2010
Sponsor Name: Teva
Meeting Requestor: Terry Duffield
Meeting Chair: Badrul A. Chowdhury
Meeting Recorder: Eunice Chung-Davies

Meeting Attendees:

FDA Attendees

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Lydia Gilbert McClain, M.D., Deputy Director, DPARP

Peter Starke, M.D., Clinical Reviewer, DPARP

Prasad Peri, Ph.D., Acting Chief, Branch VIII, ONDQA

Yun Xu, Ph.D., Acting Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II

Liang Zhao, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II

Thomas Permutt, Ph.D., Director, Division of Biometrics II

Kiya Hamilton, Ph.D., Statistics Reviewer, Division of Biometrics II

Sofia Chaudhry, M.D., Clinical Reviewer, DPARP

Eunice Chung-Davies, Pharm.D., Regulatory Management Officer, DPARP

Sponsor Attendees

Tushar Shah, M.D., Senior Vice President, Global Respiratory R&D

Paul Dorinsky, M.D., Vice President, Global Respiratory Clinical Research

Mark Lepore, M.D., Clinical Research Physician, Global Respiratory R&D

Patrick Darken, Ph.D., Senior Director, Global Biostatistics

Harald Iverson, Ph.D., Associate Director, Global Biostatistics

Denise Wayne, Ph.D., Manager, Clinical Research, Global Respiratory R&D

Steve Viti, Ph.D., Senior Director, Global Respiratory Regulatory Affairs

Axel Perlwitz, Ph.D., Associate Director, Global Respiratory Regulatory Affairs

1.0 BACKGROUND

Ms. Terry Duffield of Teva requested an End-of-Phase 2 meeting on June 29, 2010. The meeting was granted on July 9, 2010. The preliminary comments (*in italics*) were sent to Teva in response to their September 1, 2010, briefing package questions (***bold italics***) on September 28, 2010. Teva wished to clarify the Division's response to Clinical Question 2 as well as CMC Question 6. Any discussion that took place during the October 5, 2010, teleconference is in normal font.

2.0 DISCUSSION

Question 1:

Does the Agency agree that the studies proposed in the Phase 3 clinical program in the adult and adolescent population are adequate to support approval for the proposed indications?

FDA Response:

The phase 3 adult/adolescent program appears reasonable pending our review of the final phase 3 protocols. We have the following general comments:

- 1. Conduct clinical studies across diverse geographical settings in the United States, including areas that have both low and high relative humidity. This is to assess the effect of humidity and other environmental variables on the dry powder formulation of albuterol, and acceptable performance of your product in diverse settings.*
- 2. Assess robustness and reliability of Albuterol Spiromax throughout the phase 3 clinical program. All devices for which patients have noted a problem, such as clogging, or other malfunction or perceived problem, should be returned for in vitro testing to the extent possible and for evaluation of the cause of the malfunction. In addition, collect a representative number of Albuterol Spiromax with no reported problems and perform comprehensive in vitro test (e.g. emitted dose, ASPD) to assure reliability and robustness of the product. Device use and performance should also be assessed through directed questions defined in all phase 3 trials. Also, see our responses to Questions 6 and 7.*
- 3. Include protocols for the clinical and the in vitro evaluations of dose counter and device performance reliability in your phase 3 protocols.*
- 4. Consider obtaining first dose and steady state PK data at the proposed therapeutic dose in a subset of patients in one of the clinical studies for labeling purposes.*

Question 2:

Does the Agency agree with the overall design, endpoints and sample size of the adult and adolescent Phase 3 studies?

FDA Response:

In general, the overall design, endpoints, and sample size of the adult/adolescent studies appear adequate. However, we have the following comments:

- 1. You will need to ensure that there are adequate numbers of adolescents enrolled in the phase 3 studies to allow for an assessment of efficacy and safety in the subgroup of patients 12 through 16 years of age. An adequate number may generally be interpreted to mean that a representative number of patients in the age group be enrolled compared to the overall enrolled population.*
- 2. In your phase 3 chronic dose studies (ABS-AS-301 and ABS-AS-304), your calculated sample size of 75 subjects per group is acceptable. You also propose to increase your sample size to 90 subjects per group to allow for a 16% dropout rate. Assuming your analysis population consists of all randomized subjects and taking into consideration your proposal to handle missing Week 12 data, sample size need not be increased to allow for dropouts. Otherwise, increasing the sample size to 90 subjects per group is reasonable to allow adequate safety data.*

This comment also applies to your exercise-induced bronchospasm study, ABS-AS-302. Your calculated sample size of 30 subjects per group is acceptable, and increasing the sample size to 36 subjects is reasonable to allow adequate safety data.

- 3. In your phase 3 chronic dose studies, you propose to*

(b) (4)

(b) (4)

(b) (4)

In

your statistical analysis plan, discuss potential mechanisms which may cause FEV₁ data to be missing, and how those mechanisms affected your selection of the primary analysis method. We also recommend that you outline additional analyses to gauge the sensitivity of your primary analysis method to violations of the assumed missing data mechanism. In addition, provide a plan on how you will integrate and explain the results from all these sensitivity analyses; in particular, if the results are in a different direction from the result of the primary analysis.

Refer to the National Research Council of the National Academy's report, titled "The Prevention and Treatment of Missing Data in Clinical Trials" for further information.

Discussion:

Teva requested clarification with regard to the following:

"Since (b)(4) is not considered an acceptable method for handling missing data for the primary analysis of the Phase 3 chronic dosing studies, the Sponsor would like to clarify that the Agency would accept a repeated measures based analysis using FEV1 AUC0-6 above each visit's baseline value that is obtained at every clinic visit. In such an analysis, the treatment difference over the entire study (12 weeks) would be considered the primary endpoint. Since this is a maximum likelihood based analysis, it is valid for missing at random missingness, and it is one of the recommended approaches in the National Research Council report. Based on this model, the difference at each visit including Week 12 would also be estimated and evaluated as supportive analyses. Furthermore, sensitivity analyses including multiple imputation based approaches that account for the reasons for missingness, as well as the analysis of completers and per protocol populations will be included to evaluate the robustness of the primary analysis to missing data as supportive analyses. "

FDA clarified that although the repeated-measures model is probably a better way of handling dropouts (b)(4) we have been primarily interested in the outcome at 12 weeks rather than the mean over time. The 12-week outcome can be estimated within the repeated-measures model. Teva noted that they would have more power if the average was used.

FDA stated that they acknowledge that the drug in the study is albuterol and that we know albuterol is effective but this is ensuring that the sponsor's drug product combination is effective. The comments regarding how to handle missing data are minor nuances compared to the larger scope of things. FDA stated that we do not have a really strong view regarding what Teva decides to use as primary or secondary endpoints; however, Teva should look at the first dose and the last dose, and compare the first and last dose. If there is a loss of efficacy, the sponsor needs to determine what is going on. Also, the chronic dosing will assess whether there is tachyphylaxis.

4. *In your phase 3 studies, clearly document the reasons for study discontinuation and avoid the use of vague terms such as 'lost to follow-up', 'patient/investigator decision,' 'withdrawn consent', etc. Include a plan for attempting to contact patients that are "lost to follow- up" so that a more informative category can be assigned.*
5. *Include a statistical analysis plan when you submit your phase 3 protocols. Include details of any multiplicity adjustments for your secondary endpoints, particularly if you want to include them in the label.*

Question 3:

Does the Agency agree with the overall design, endpoints and sample size of the long term safety study?

FDA Response:

Pending review of safety signals in the rest of the clinical program, the overall design, endpoints and sample size of the proposed long-term safety study appear reasonable. See our response to Question 1 (Comments # 1 - 3).

Question 4:

Does the Agency agree that a single study in exercise-induced bronchospasm is adequate to support an indication of EIB in the adult and adolescent population?

FDA Response:

Acceptance of one study for an EIB indication is based on a determination of efficacy and safety from studies performed to support the indication of treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease. A single study in exercise-induced bronchospasm may be adequate if the proposed studies support approval for an indication of reversible obstructive airway disease.

Question 5:

Does the Agency agree that the dose counter assessments in the 12-week QID dosing period of the long term safety study are adequate for evaluating the counter performance in the clinical study?

FDA Response:

It is premature to answer this question. See our response to Question 1 (Comment # 3).

Question 6:

Does the Agency agree that the planned assessments of device durability in the Phase 3 program (particularly in the long term safety study) are adequate and sufficient for evaluating the device durability in the clinical study?

FDA Response:

We do not agree with the proposed device durability assessments. See our response to Question 1 (Comments # 2 and 3) as well as the following additional comments:

- 1. Your proposal to have all devices returned and to take a random sample of 50 devices after about 3 weeks of regular use in the first 12 weeks of the study, and 50 devices after unspecified p.r.n (as needed) use in the second 40 weeks of the study is not acceptable.*

Discussion:

Teva requested clarification with regard to the following:

"All study inhalers from the Phase 3 long term safety study will be routinely returned (during both the QID and PRN dosing periods) when approximately 85% (170 of 200) of the doses have been dispensed. During the QID dosing period, the inhalers will be in use for approximately three weeks (corresponding to approximately 85% of the doses used) while during the PRN dosing period, inhalers will be in use for varying periods of time based on individual use. However, in this portion of the study, inhalers will also be returned when approximately 85% of the doses have been used. This will result in inhalers having been in use for 1-8 months before the targeted number of doses has been used. In addition, in all studies in the phase 3 clinical development program, any inhaler with a reported problem and any failed devices will be returned to the site of manufacture for evaluation.

Considering the above clarification of the testing plans, can the Agency please clarify what aspect of the plan was unacceptable; that is, whether the number of devices being tested (i.e. 50 devices in each of the 2 study periods, for a total of 100 devices) was unacceptable and should have been 100 devices from each study period (QID and PRN studies, resulting in 200 inhalers tested overall), or whether some other aspect of the plan was unacceptable? "

The Agency stated that, based on clarification that was provided, the sponsor's proposal for using 100 devices is adequate. The point that was not clear in the briefing package was at what time point/s devices would be returned for testing in a PRN study. However, FDA stated that we have no issue with Teva's proposal, as clarified. FDA encouraged Teva to plan ahead to submit their protocols so that FDA has ample time to review and provide feedback before starting the study. Teva agreed to keep this in mind as they submit their protocols.

2. *All failed devices and devices for which patients have reported a problem should be returned for evaluation and in vitro testing to the extent possible.*
3. *A representative sample of devices should be evaluated by in vitro performance testing near the end of the life of the device to ensure ruggedness throughout the product's intended span of use. Such testing is generally performed in at least 100 devices towards the end of device life, leaving enough doses that will be necessary for performing in vitro tests.*

Question 7:

Does the Agency confirm that the described plan for selection of inhalers and post-clinical testing of inhaler performance is sufficient to demonstrate inhaler durability and reliability?

FDA Response:

We do not agree. See our response to Question 6.

Question 8:

Based on the successful demonstration in the Phase 1 ABS-AS-101 and Phase 2 ABS-AS-201 studies that systemic exposure following Albuterol Spiromax in adults is similar to the marketed product, ProAir HFA, and that the safety, efficacy and pharmacodynamic effects of Albuterol Spiromax in adults are similar to ProAir HFA, does the Agency agree that Teva can initiate the pediatric pharmacokinetic study (Phase 1, ABS-AS-102) and the pediatric single dose, dose-ranging study (Phase 2, ABS-AS-202) without waiting for completion of the Phase 3 program in adults and adolescents?

FDA Response:

We agree.

Question 9:

Does the Agency agree that the Phase 1 pediatric (4 to 11 years old) study is adequate for the evaluation of systemic exposure of Albuterol Spiromax?

FDA Response:

Your proposal appears adequate.

Question 10:

Does the Agency agree with the overall design, endpoints and sample sizes of the Phase 1 and Phase 2 pediatric studies?

FDA Response:

Your proposal appears adequate.

Question 11:

Does the Agency agree with the proposed overall safety evaluations for Albuterol Spiromax in the clinical program?

FDA Response:

A key component of the overall safety evaluations for Albuterol Spiromax is the assessment of the device reliability and performance. See our comments regarding evaluation of device performance and reliability in our responses to Questions 1, 6, and 7.

Question 12:

Does the Agency agree that the extent of exposure to Albuterol Spiromax in the proposed development program is adequate to support approval in the adult and adolescent population?

FDA Response:

Your proposal appears reasonable, although a final determination cannot be made until the data are reviewed. Also, see our response to Question 2 (Comment # 2) regarding the sample size.

Question 13:

Does the Agency agree that the proposed clinical program in the adult and adolescent population is adequate to support the proposed indication in this age group (treatment or prevention of bronchospasm in patients with reversible obstructive airway disease)?

FDA Response:

Your proposal appears reasonable, although a final determination cannot be made until the data are reviewed.

Question 14:

Does the Agency agree that successful outcome of the proposed clinical program will be adequate to gain the same Adult and Adolescent Indication as ProAir HFA (i.e., "... indicated in patients 12 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 12 years of age and older")?

FDA Response:

Your proposal appears reasonable, although a final determination cannot be made until the data are reviewed.

Question 15:

Does the Agency agree with the selection of the 90-mcg dose strength for full clinical development in the adult and adolescent population and for the Phase 1 and Phase 2 clinical studies in the pediatric populations?

FDA Response:

Your proposal for selection of a 90-mcg dose strength for patients 4-11 years of age appears reasonable.

ADDITIONAL COMMENTS:

Nonclinical:

The impurity, (b) (4) a compound with a structure alert has been identified in your drug substance and drug product with specifications NMT (b) (4) % in your drug substance and NMT (b) (4) % in your drug product. For your NDA submission, reduce the levels of (b) (4) in accordance with the Genotoxic Impurities Guidance. If this is not possible, conduct an appropriate genotoxicity assay (i.e., Ames assay to qualify the impurity).

For your NDA submission, monitor impurities and degradation products of all active ingredients and refer to ICH Guidance [ICH Q3A(R) and ICH Q3B(R)] for possible qualification requirements. Impurities or degradants of active ingredients, that are identified as structural alerts should be at or below acceptable qualification thresholds to support an NDA, as described in the draft FDA Guidance for Industry "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008)".

3.0 ISSUES REQUIRING FURTHER DISCUSSION

N/A

4.0 ACTION ITEMS

N/A

5.0 ATTACHMENTS AND HANDOUTS

N/A

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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/

EUNICE H CHUNG-DAVIES
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