DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761033/Original # 1

BLA APPROVAL

Teva Respiratory, LLC
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs

Dear Ms. Kampf:

Please refer to your Biologics License Application (BLA) dated March 29, 2015, received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for Cinqair (reslizumab).

BLA 761033 provides for the use of Cinqair (reslizumab) for the following indications which, for administrative purposes, we have designated as follows:

- BLA 761033/Original #1 - To reduce exacerbations, relieve symptoms, and improve lung function in patients 18 years of age and older with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.

(b) (4)

The subject of this action letter is BLA 761033/Original #1. (b) (4)

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2047 to Teva Respiratory LLC, Frazer, Pennsylvania under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Cinqair (reslizumab) indicated to reduce exacerbations, relieve symptoms, and improve lung function in patients 18 years of age and older with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.

MANUFACTURING LOCATIONS
Under this license, you are approved to manufacture Cinqair drug substance at (b) (4) The final formulated product will be manufactured, filled, labeled, and packaged at (b) (4) You may label your product with the proprietary name, Cinqair, and will market in 10 mL vials.

DATING PERIOD
The dating period for Cinqair shall be 36 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

FDA LOT RELEASE
You are not currently required to submit samples of future lots of Cinqair to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Cinqair, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING
We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING
As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS
Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product

Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for Approved BLA 761033**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 note that you have fulfilled the pediatric study requirement for ages 12 to 17 years for this application.

We are waiving the pediatric study requirement for ages zero to 11 years because there is evidence strongly suggesting that the drug product would be ineffective in this pediatric group. Reslizumab was not found to be effective in children 12 to 17 years of age.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of anaphylaxis.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3053-1: Develop and validate an assay that is sufficiently sensitive, selective, and specific to reliably detect product specific antibodies of the IgE isotype.

The timetable you submitted on January 19, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: December 2016

3053-2: Use the anti-reslizumab IgE assay developed under 3053-1 to test serum samples from patients who had treatment associated anaphylaxis.

The timetable you submitted on January 19, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: March 2017

3053-3: Submit a qualification report demonstrating the suitability of the commercial anti-alpha gal ELISA from (b) (4) that was used to analyze the sera of the four treatment-related anaphylaxis patients.

The timetable you submitted on January 19, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: April 2016

Submit the protocols to your IND 101399, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3053-4: Develop and validate an assay to detect anti-drug antibodies that neutralize reslizumab activity. The assay should be sufficiently sensitive, selective, and specific to reliably detect neutralizing anti-drug antibodies.

The timetable you submitted on January 19, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: March 2017

3053-5: To use the assay developed and validated under 3053-4 to detect anti-reslizumab neutralizing antibodies in sera from confirmed anti-drug antibody positive asthmatic patients.

The timetable you submitted on January 19, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: August 2017

3053-6: To implement a (b) (4) (b) (4) in the drug substance manufacturing process. The final study report(s) will be submitted according to 21 CFR 601.12.

The timetable you submitted on February 17, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: May 2017

3053-7: Re-evaluate and tighten the (b) (4) endotoxin acceptance criteria for the (b) (4) (b) (4) samples after manufacturing 30 batches of reslizumab.

The timetable you submitted on January 19, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: June 2019

3053-8: Establish a hold time limit for the intermediate (b) (4) hese hold times should be validated at scale to demonstrate that these (b) (4) can be held under proposed worst-case conditions without compromising the microbial quality of the product.

The timetable you submitted on January 19, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: April 2017

3053-9: To develop, validate and establish an identity test for incoming bulk drug substance to the drug product manufacturing site that uniquely confirms identity of reslizumab. The final study report(s) will be reported according to 21 CFR 601.12.

The timetable you submitted on January 19, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: June 2016

3053-10: To reduce the vial over fill to comply with USP <1151> recommendations. Provide information to demonstrate fill consistency at the revised volume. The final study report(s) will be reported according to 21 CFR 601.12.

The timetable you submitted on January 19, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: December 2016

3053-11: Requalify the dye ingress container closure integrity (CCI) test method with reslizumab 10 mL/20 mm vial under worst case challenge conditions using positive controls with a breaches of ≤ (b) (4) μm in size and submit the data in accordance with 21 CFR 601.12.

The timetable you submitted on January 19, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: April 2016

3053-12: Qualify the microbial retention study at routine manufacturing /room temperature and submit the results in accordance with 21 CFR 601.12.

The timetable you submitted on January 19, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: June 2016

3053-13: To evaluate and revise, as needed, the acceptance criteria for all the drug substance and drug product release and stability specifications based on data from at least thirty released lots of reslizumab drug substance and drug product. The final study report(s) will be submitted according to 21 CFR 601.12.

The timetable you submitted on January 19, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: June 2019

3053-14: To improve the overall control strategy of the drug substance manufacturing process [redacted] (b) (4)

The timetable you submitted on January 19, 2016, states that you will conduct this study according to the following schedule:

Final report submission date: July 2017

Submit clinical protocols to your IND 101399 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, MD, MPH
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES: Content of Labeling
Carton and Container Labeling

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

/s/

CURTIS J ROSEBRAUGH
03/23/2016