DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761058

BLA APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Christopher Dougherty, PhD, MS
Senior Associate Director, Regulatory Affairs Biosimilars

Dear Dr. Dougherty:

Please refer to your Biologics License Application (BLA) dated October 27, 2016, received October 27, 2016, and your amendments, submitted under section 351(k) of the Public Health Service Act for Cyltezo (adalimumab-adbm) Injection, 40 mg/0.8 mL.

LICENSING

We have approved your BLA for Cyltezo (adalimumab-adbm) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Cyltezo under your existing Department of Health and Human Services U.S. License No. 2006. Cyltezo is indicated for:

1. Rheumatoid Arthritis (RA):
   - reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.

2. Juvenile Idiopathic Arthritis (JIA):
   - reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years of age and older.

3. Psoriatic Arthritis (PsA):
   - reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis.

4. Ankylosing Spondylitis (AS):
   - reducing signs and symptoms in adult patients with active ankylosing spondylitis.

5. Adult Crohn's Disease (CD):

- reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
- reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

6. Ulcerative Colitis (UC):
   - inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP).

7. Plaque Psoriasis (Ps):
   - the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Cyltezo at your facility in Fremont, CA. You may label your product with the proprietary name, Cyltezo, and will market it in 40 mg/0.8 mL Prefilled Syringe.

DATING PERIOD

The dating period for Cyltezo shall be 24 months from the date of manufacture when stored at 5 °C ± 3 °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 Cyltezo 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 Cyltezo, 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.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 CFR 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, text for the Instructions for use, Medication Guide). 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 — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (May 2015, Revision 3). For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 761058**." Approval of this submission by FDA is not required before the labeling is used.

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.

The following comments pertain to Rheumatoid Arthritis indication:

> We are waiving the pediatric studies requirement for the Polyarticular Juvenile Idiopathic Arthritis (pJIA) in pediatric patients 0 to less than 2 years of age because necessary studies are impossible or highly impracticable given that the disease is rarely diagnosed in this population.

We are deferring the required pediatric assessment for pediatric patients 2 years to less than 4 years of age. See Deferred Pediatric Assessments below.

We are deferring the required pediatric assessment for patients < 30 kg. See Deferred Pediatric Assessments below.

The following comment pertains to Psoriatic Arthritis indication:

We are waiving the pediatric study requirements for pediatric patients 0 to 17 years of age for this indication because necessary studies are impossible or highly impracticable.

The following comment pertains to Ankylosing Spondylitis indication:

We are waiving the pediatric study requirements for pediatric patients 0 to 17 years of age for this indication because necessary studies are impossible or highly impracticable.

The following comments pertain to Crohn's Disease indication:

We are waiving the pediatric study requirements for pediatric patients with Crohn's disease less than 6 years of age because necessary studies for this product (i.e., dedicated studies limited to pediatric patients 2 years to less than 6 years of age) are impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age.

We are deferring the required pediatric assessment for pediatric patients 6 years to 17 years of age. See Deferred Pediatric Assessments below.

The following comments pertain to Ulcerative Colitis indication:

We are waiving the pediatric study requirements for pediatric patients with ulcerative colitis less than 5 years of age because necessary studies for this product (i.e., dedicated studies limited to pediatric patients 2 years to less than 5 years of age) are impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age.

We are deferring the required pediatric assessment for pediatric patients 5 to 17 years of age. See Deferred Pediatric Assessments below.

The following comment pertains to Plaque Psoriasis indication:

We are waiving the pediatric study requirements for pediatric patients 0 to 17 years of age for this indication because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and is not likely to be used in a substantial number of pediatric patients.

Deferred Pediatric Assessments

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(C) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

3260-1 Assessment of Cyltezo (adalimumab-adbm) for the treatment of Polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years to less than 4 years of age.

The timetable you submitted on August 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission Date: September 2021

3260-2 Assessment of Cyltezo (adalimumab-adbm) for the treatment of pediatric Crohn's disease in pediatric patients 6 years to 17 years of age.

The timetable you submitted on August 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission Date: September 2021

3260-3 Assessment of Cyltezo (adalimumab-adbm) for the treatment of pediatric ulcerative colitis in pediatric patients 5 years to 17 years of age.

The timetable you submitted on August 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission Date: December 2020

3260-4 Develop a presentation that can be used to accurately administer Cyltezo (adalimumab-adbm) to pediatric patients who weigh less than 30 kg.

The timetable you submitted on August 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission Date: September 2021

Submit the protocols to your IND 110467, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark

your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

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

We remind you of your postmarketing commitments:

3260-5 Develop a comprehensive and robust control strategy to control for effector function of BI 695501.

The timetable you submitted on August 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2018

3260-6 Conduct the (b) (4) in-process and release method qualification using two additional batches of BI 695501.

The timetable you submitted on August 17, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission August 2018

Submit clinical protocols to your IND 110467 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

If you have any questions, call Sadaf Nabavian, Senior Regulatory Project Manager, at (301) 796-2777.

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

ENCLOSURE(S):
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/

BADRUL A CHOWDHURY
08/25/2017