DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761046

BLA APPROVAL

Merck Sharp & Dohme Corp., a subsidiary of Merck and Co., Inc.
Attention: Donnette D. Staas, PhD
Director, Global Regulatory Affairs
351 Sumneytown Pike
UG2D-68
North Wales, PA 19454-2504

Dear Dr. Staas:

Please refer to your Biologics License Application (BLA) dated November 17, 2015, received November 23, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for Zinplava (bezlotoxumab) Injection, 1,000 mg/40 mL.

We acknowledge receipt of your major amendment dated June 30, 2016, which extended the goal date by three months.

LICENSING

We have approved your BLA for Zinplava (bezlotoxumab) effective on this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Zinplava under your existing Department of Health and Human Services U.S. License No. 0002. Zinplava is indicated to reduce recurrence of *Clostridium difficile* infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture bezlotoxumab drug substance at (b) (4) . The final formulated product will be manufactured, filled, labeled and packaged at MSD Ireland, Carlow, Ireland. You may label your product with the proprietary name, Zinplava, and will market it in 1000 mg/40 mL Injection in a single-dose vial.

DATING PERIOD

The dating period for Zinplava shall be 24 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 a (b) (4) °C.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Zinplava 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 Zinplava, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended and 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 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 submitted on September 27, 2016, and May 9, 2016, respectively 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)". 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 761046**." 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 are waiving the pediatric study requirement for patients < 1 year of age because necessary studies are impossible or highly impractical as the disease does not occur commonly in this population.

We are deferring submission of your pediatric studies for patients ≥ 1 year to <18 years of age because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required post-marketing study. The status of this post-marketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. The required study is listed below.

3118-1: Conduct a randomized, double-blind, placebo-controlled trial of safety, efficacy, and pharmacokinetics of Zinplava (bezlotoxumab) in pediatric patients from 1 to less than 18 years of age receiving antibacterial therapy for *C. difficile* infection.

Final protocol submission:	April 2017
Trial completion:	May 2022
Final report submission:	November 2022

Submit the protocol(s) to your IND 12823, with a cross-reference letter to this BLA.

Reports of this required pediatric post-marketing study 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 the study. When submitting the report, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENT**" 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 post-marketing commitments:

3118-2: Perform low endotoxin recovery studies [redacted (b) (4)] Use an endotoxin standard as the spiking material.

The timetable you submitted on October 18, 2016, states that you will provide a final report on the outcome of these studies according to the following schedule:

Final Report Submission: December 2016

3118-3: Repeat the microbial retention study using a more suitable surrogate solution. Attributes of the surrogate solution that are known to affect microbial retention (surface tension, viscosity, ionic strength, etc.) should model the drug product as closely as possible while preserving viability of the challenge organism. Alternatively, use of a reduced exposure time or modified process conditions (e.g., temperature) may be appropriate. Provide the summary data, the associated report, and justification for any modifications to the study. If any [redacted (b) (4)] parameters are changed as a result of the study, update the BLA file accordingly.

The timetable you submitted on October 18, 2016, states that you will provide a final report on the outcome of this study according to the following schedule:

Final Report Submission: March 2017

3118-4: Perform additional testing to support the clonality of the bezlotoxumab master cell bank (MCB).

The timetable you submitted on October 19, 2016, states that you will provide a final report on the outcome of this study according to the following schedule:

Final Report Submission: October 2017

3118-5: Conduct a study to support the worst case cumulative hold times in the bezlotoxumab drug substance manufacturing process to demonstrate that the worst case cumulative hold time will not adversely affect the product quality of bezlotoxumab drug substance. These data are expected to demonstrate that there is no adverse impact to product quality [redacted (b) (4)]

The timetable you submitted on October 19, 2016, states that you will provide a final report on the outcome of this study according to the following schedule:

Final Report Submission: October 2017

3118-6: Develop a valid *in vitro* endotoxin assay for drug product release testing. Conduct studies to evaluate sample preparation, sample pre-treatment, and alternative test methods for endotoxin detection.

The timetable you submitted on October 18, 2016, states that you will provide a final report on the outcome of these studies according to the following schedule:

Final Report Submission: July 2018

3118-7: Re-evaluate MK-6072 drug substance (DS) and drug product (DP) lot release and stability specifications after a minimum of 30 DS lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

The timetable you submitted on October 18, 2016, states that you will provide a final report on the outcome of this study according to the following schedule:

Final Report Submission: December 2023

Submit clinical protocols to your IND 12823 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all post-marketing 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 post-marketing 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 post-marketing commitments should be prominently labeled "**Post-marketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Post-marketing 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.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has also contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF 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 reports. 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 this evaluation.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, MD, MPH
Director
Office of Antimicrobial Products
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/

EDWARD M COX
10/21/2016