Our STN: BL 125613/0

**BLA APPROVAL**
August 23, 2017

Kamada Ltd.
Attention: Ms. Holli S. Vaughan
Biologics Consulting Group, Inc.
400 North Washington Street, Suite 100
Alexandria, VA 22314

Dear Ms. Vaughan:

Please refer to your Biologics License Application (BLA) for Rabies Immune Globulin (Human) dated August 29, 2016, received August 29, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act).

We have approved your BLA for Rabies Immune Globulin (Human) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Rabies Immune Globulin (Human) under your existing Department of Health and Human Services U.S. License No. 1826. Rabies Immune Globulin (Human) is indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. Rabies Immune Globulin (Human) should be administered concurrently with a full course of rabies vaccine.

The review of this product was associated with the following National Clinical Trial (NCT) number: NCT02040090.

Under this license, you are approved to manufacture Rabies Immune Globulin (Human) drug substance at Kamada Ltd., MP Negev, Beit Kama, Israel 8532500.

You may label your product with the proprietary name KEDRAB and market it in 2 mL product fill (in 4 mL vial size) and 10 mL product fill (in 13.5 mL vial size) vials with a potency 150IU/mL.

You must label your product with the proper name Rabies Immune Globulin (Human) that we have approved, and market it as approved in your license application.

We did not refer your application to the Blood Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

## DATING PERIOD

The dating period for Rabies Immune Globulin (Human) shall be 30 months from the date of manufacture when stored at 5±3°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be (b) (4) when stored at (b) (4).

## FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

## BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, 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 the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
WO71-G112
Silver Spring, MD 20993-0002

## MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Rabies Immune Globulin (Human) or in the manufacturing facilities.

## LABELING

We hereby approve the draft package insert labeling submitted under amendment 34, dated August 23, 2107, and the draft carton and container labeling submitted under STN 126513/0 dated August 29, 2016.

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. All final labeling should be submitted as Product Correspondence to this BLA 125613 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

**ADVERSE EVENT REPORTING**

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format — Postmarketing Safety Reports* at http://www.fda.gov/Drugs/DrugSafety/ucm400526.htm and FDA's Adverse Event reporting System website http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

In addition, you must submit adverse event reports for any infectious disease transmission within 15 days after learning of the event. Infectious disease transmission refers to an adverse event that involves suspected or confirmed transmission of an infectious agent, whether the recipient develops the infectious disease or only has serologic or other evidence. If an infectious disease transmission event is serious and unexpected, you must submit a 15-day "alert report," as required under 21 CFR 600.80 (c)(1)(i). Infectious disease transmission events that do not meet criteria for expedited submission require periodic reports and must be submitted as individual case reports safety within 15 days, as authorized under 21 CFR 600.80(c)(2)(i). You should submit reports for all other non-expedited adverse events under the periodic reporting requirements specified in 21 CFR 600.80(c)(2).

**PEDIATRIC 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric study for ages 0 months to <17 years years for this application because:

1) This product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an "**Annual Status Report of Postmarketing Study Requirement/Commitments**" and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. This required study is listed below:

1. Deferred pediatric study under PREA for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and concurrently with a full course of rabies vaccine in pediatric patients ages 0 months to <17 years.

   Final Protocol Submission: December 14, 2016

Study Initiation Date: March 31, 2017

Study Completion Date: June 15, 2020

Final Report Submission: January 15, 2021

Submit final study reports to this BLA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated as:

- **Required Pediatric Assessment**

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIRMENTS UNDER SECTION 506B**

We acknowledge your written commitments as described in your letter of August 15, 2017, as outlined below:

2. Kamada commits to perform full scale validation on (b) (4) full scale lots, (b) (4) of the critical operating parameter ranges and times, including the (b) (4) for the (b) (4) step, with in-process testing for (b) (4) at each manufacturing step.

   Kamada will submit a validation protocol outlining the operating parameters for each lot, and (b) (4) tests along with the acceptance criteria, as a Post marketing Commitment – Product Correspondence prior to manufacture of these lots. The final report will be submitted as a Post Marketing Commitment – Final Study Report by August 31, 2018.

   These lots will be placed on stability and a final stability report will be submitted as a Postmarketing Commitment – Final Study Report by February 28, 2022.

   Final Protocol Submission: October 31, 2017

   Final Report Submission: August 31, 2018

   Final Stability Report Submission: February 28, 2022

3. Kamada commits to perform validation of an improved (b) (4) method and determine the (b) (4) specifications accordingly.

   A final validation report as well as the method SOP and specifications will be submitted to FDA by October 31, 2017, as a CBE-30 Supplement. In case a method different from that provided by CBER is chosen for the validation, a full characterization of the (b) (4) will be performed.

   The final method specification will include (b) (4)

The submission will include the acceptance criteria for (b) (4) .

Final Report Submission: October 31, 2017

4. Kamada commits to perform validation of the container closure integrity test for each stopper and vial combination (2 ml product fill (in 4 ml vial size) and 10 ml product fill (in 13.5 ml vial) size vials and stoppers, from each of two vendors) with the inclusion of a (b) (4) . Kamada will submit a final validation report.

   Final Report Submission: December 29, 2017

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to BLA STN BL 125613/0. Please refer to the sequential number for each commitment.

Please use the following designators in your cover letter and 356h form to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Commitment – Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment – Final Study Report**.

**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 committee. 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 committee will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

Sincerely yours,

Wilson W. Bryan, MD
Director
Offfice of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research