Our STN: BL 125590/0

BLA APPROVAL
April 1, 2019

ADMA Biologics, Inc.
Attention: Mr. James Maloney
5800 Park of Commerce Boulevard, N.W.
Boca Raton, FL 33487

Dear Mr. Maloney:

Please refer to your Biologics License Application (BLA) submitted on July 31, 2015, and received on July 31, 2015, under section 351(a) of the Public Health Service Act (PHS Act) for Immune Globulin Intravenous, Human-slra.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2019 to ADMA Biologics, Inc., Boca Raton, FL, under the provisions of section 351(a) of the PHS 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 Immune Globulin Intravenous, Human-slra which is indicated for the treatment of primary humoral immunodeficiency in adults and adolescents (12 to 17 years of age).

The review of this product was associated with the following National Clinical Trial (NCT) number 01814800.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Immune Globulin Intravenous, Human-slra at your drug substance manufacturing facility located at Boca Raton, FL, your contract fill/finish facility - (b) (4) , and your contract labeling and packaging facility in (b) (4)
You may label your product with the proprietary name ASCENIV and market it in 50-mL vials.

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 Immune Globulin Intravenous, Human-slra 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. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency.

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 Ave.
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 Immune Globulin Intravenous, Human-slra, or in the manufacturing facilities.

LABELING

We hereby approve the draft package insert labeling, and the draft carton and container labeling, submitted under Amendment 71, dated March 29, 2019.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (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.

The SPL will be accessible via publicly available labeling repositories.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels that are identical to the package and container labels submitted on March 29, 2019, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

All final labeling should be submitted as Product Correspondence to this BLA 125590 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

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 Ave.
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 https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm458559.pdf and FDA's Adverse Event reporting System website at 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 safety case reports 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 waiving the pediatric study requirement for ages 0 to less than 2 years because necessary studies are impossible or highly impracticable, due to the rarity of primary humoral immunodeficiency diagnosed in this age group.

We are deferring submission of your pediatric study for ages 2 to 12 years for this application because this product is ready for approval for use in adults and adolescents 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. The required study is listed below:

1. Deferred pediatric study under PREA for the treatment of primary immunodeficiency in pediatric patients ages 2 to 12 years.

   Final Protocol Submission: December 31, 2019

   Study Completion Date: December 31, 2022

   Final Report Submission: June 30, 2023

Submit the protocol to your IND 15308, with a cross-reference letter to this BLA, STN BL 125590, explaining that this protocol was submitted to the IND.

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 REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letter of March 22, 2019, as outlined below:

2. ADMA commits to implementing the alert limit of (b) (4) for the (b) (4) prior to the manufacture of the next lot of ASCENIV, 10% IGIV. ADMA will report the implementation as a "Postmarketing Commitment – Status Update."

   Final Report Submission: April 30, 2020

3. ADMA commits to reporting the results of bioburden testing of (b) (4) for manufacturing of future lots of ASCENIV, 10% IGIV as a "Postmarketing Commitment – Status Update."

   Final Report Submission: April 30, 2020

4. ADMA commits to conducting a comprehensive study of (b) (4) of ASCENIV, 10% IGIV, using the samples held at (b) (4) Both samples will be tested for (b) (4) to generate real-time concordance data. The final study reports will be submitted as a "Postmarketing Commitment – Final Study Report" by April 30, 2020.

   Final Report Submission: April 30, 2020

5. ADMA commits to submitting information on the ongoing stability study, SP-DF-3093, annually as a "Postmarketing Commitment – Status Update." The final stability report will be submitted as a "Postmarketing Commitment – Final Study Report" by June 30, 2020. ADMA will also report any confirmed out-of-specification results at the recommended storage condition from the stability monitoring to the Agency within 45 days of the event(s).

   Final Report Submission: June 30, 2020

6. ADMA commits to resetting the lot release specification for (b) (4) using the approved manufacturing process. The final study report will be submitted as a CBE-30 by December 31, 2020.

   Final Report Submission: December 31, 2020

We request that you submit information concerning nonclinical and chemistry, manufacturing, and controls postmarketing commitments and final reports to your BLA, STN BL 125590. Please refer to the sequential number for each commitment.

Please use the following designators 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**.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance and
Biologics Quality
Center for Biologics
Evaluation and Research

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