DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

December 8, 2015

Our STN: BL 125577/0 **BLA APPROVAL**

Baxalta US Inc.
Attention: Maximilian Fernandez, PhD
One Baxter Way
Westlake Village, CA 91362

Dear Dr. Fernandez:

Please refer to your Biologics License Application (BLA) for von Willebrand factor (Recombinant), dated and received December 19, 2014, submitted under section 351(a) of the Public Health Service Act (PHS Act).

LICENSING

We have approved your biologics license application (BLA) for von Willebrand factor (Recombinant) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, von Willebrand factor (Recombinant) under your existing Department of Health and Human Services U.S. License No. 2020. Von Willebrand factor (Recombinant) is indicated for on-demand treatment and control of bleeding episodes in adults diagnosed with von Willebrand disease (VWD).

The review of this product was associated with the following National Clinical Trial (NCT) number: 01410227.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture von Willebrand factor (Recombinant) bulk drug substance [redacted] The final formulated product will be manufactured, filled, labeled and packaged at Baxalta U.S. Inc., Thousand Oaks, California, USA. The diluent, sterile Water for Injection (sWFI) will be manufactured at [redacted]

You may label your product with the proprietary name VONVENDI and will market it in single-use vials containing approximately 650 or 1300 international units (IU) of von Willebrand factor activity as determined by the Ristocetin cofactor (VWF:RCo) assay. The product will be reconstituted with the provided sWFI for intravenous administration.

ADVISORY COMMITTEE

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 which would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for the final drug product (FDP) of von Willebrand factor (Recombinant) shall be 36 months from the date of manufacture when stored at +5 °C ± 3 °C. Within this period, the FDP may be stored at room temperature (not to exceed +30 °C) for up to 12 months. 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 bulk drug substance shall be

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of von Willebrand factor (Recombinant) to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). 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.

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, 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 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 von Willebrand factor (Recombinant), or in the manufacturing facilities.

LABELING

We hereby approve the draft package insert labeling submitted under amendment 30, dated December 4, 2015 and the draft carton and container labeling submitted under amendment 31, dated December 7, 2015.

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. In addition, please submit three original paper copies for carton and container final printed labeling. All final labeling should be submitted as Product Correspondence to this BLA 125577 at the time of use (prior to marketing) and include implementation information on FDA Form 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 titled, "*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 an FDA Form 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 advertisement 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.

Because the biological product for this indication has an orphan drug designation, you are exempt from this requirement.

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 biological products 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 biological products 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, please contact 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.

Sincerely yours,

for
Jay S. Epstein, MD
Director
Office of Blood Research and Review
Center for Biologics Evaluation and Research