DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125562/0

BLA APPROVAL - ANIMAL RULE

Cangene Corporation
Attention: Ms. Allison Kennedy
155 Innovation Drive
Winnipeg, Manitoba R3T 5Y3
Canada

Dear Ms. Kennedy:

We have approved your biologics license application for Anthrax Immune Globulin (Human) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Anthrax Immune Globulin (Human) under your existing Department of Health and Human Services U.S. License No. 1201. Anthrax Immune Globulin (Human) is indicated for the treatment of inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs.

Under this authorization, you are approved to manufacture Anthrax Immune Globulin (Human) at your facility in Winnipeg, Manitoba, Canada. You may label your product with the proprietary name Anthrasil™ and will market it in 50 ml (b) (4) glass 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 designs and trial results, did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

The dating period for Anthrax Immune Globulin (Human) shall be 72 months from the date of manufacture when stored at ≤ -15°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

You currently are not required to submit samples of future lots of Anthrax Immune Globulin (Human) to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, 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.

You must submit information to your biologics license application 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 Anthrax Immune Globulin (Human), or in the manufacturing facilities.

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

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 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. You should submit postmarketing adverse experience reports and distribution reports to the Office of Biostatistics and Epidemiology, at 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

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

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 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.

SUBPART H APPROVAL REQUIREMENTS

Approvals under 21 CFR Part 601, Subpart H (Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible) are subject to three requirements:

1. *Approval with restrictions to ensure safe use.*

   This subsection permits the Agency to require postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product. We have concluded that Anthrax Immune Globulin (Human) can be safely used without restrictions on distribution or use.

2. *Information to be provided to patient recipients.*

   This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart. We have concluded that the FDA-Approved Patient Labeling for Anthrax Immune Globulin (Human) meets the requirements of this subsection. We remind you that the Patient Labeling must be available with the product to be provided, when possible, prior to administration or dispensing of the drug product for the use approved under this subpart.

3. *Postmarketing Studies.*

   This subsection requires you to conduct postmarketing studies, such as field studies, to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical.

   We refer to your amendments dated December 15, 2014, February 9, 2015, and March 04, 2015, stating that you agree to conduct a field study to evaluate the efficacy, pharmacokinetics, and safety of Anthrax Immune Globulin (Human) use for the treatment of toxemia due to inhalation anthrax:

   1. Conduct a field study (protocol AX-003A) to evaluate the efficacy, pharmacokinetics, and safety of Anthrax Immune Globulin (Human) for the treatment of toxemia associated with inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs. The primary endpoint of this study will be all-cause mortality.

      Final Protocol Submission: October 31, 2015

      Completion of Enrollment: To be determined in consultation with FDA should a broad anthrax exposure event occur.

      Completion of Data Collection: 9 months after last Anthrax Immune Globulin (Human) administration following a broad anthrax exposure event.

      Study Completion: 12 months after last Anthrax Immune Globulin (Human) administration following a broad anthrax exposure event.

      Final Report Submission: 15 months after last Anthrax Immune Globulin (Human) administration following a broad anthrax exposure event.

2. To submit annual progress reports as well as interim clinical summary reports including available cumulative clinical and pharmacokinetic data every three years from use of Anthrax Immune Globulin (Human) in sporadic systemic anthrax cases (protocol AX-003B).

   Final Protocol Submission: October 31, 2015

   Completion of Enrollment: To be determined in consultation with FDA.

   Completion of Data Collection: To be determined.

   Study Completion: To be determined.

   Final Report Submission: 9 years after final protocol approval.

Please submit the protocols to your IND 11982, with a cross-reference letter to this BLA. Submit all final reports to this BLA as a supplemental application. For administrative purposes, all submissions related to this/these required Subpart H postmarketing studies must be clearly designated as:

- **Required Postmarketing Protocol - Subpart H Postmarketing Requirements**
- **Required Postmarketing Correspondence - Subpart H Postmarketing Requirements**
- **Required Postmarketing Final Report - Subpart H Postmarketing Requirements**

Your Subpart H studies required under 601.91(b)(1) are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.70. Label your annual report an "**Annual Status Report of Postmarketing Study Requirement/ Commitments**."

AGREED UPON POSTMARKETING COMMITMENTS

We acknowledge your written commitments as described in your letter of March 17, 2015 and documented in the teleconference minutes from March 19, 2015, as outlined below:

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

3. Cangene commits to (b) (4) Manufacturing will commence pending the availability of funding for the production run(s), and this change will be submitted, with validation data, as a CBE-30 within 5 months of completion of the run(s) or by March 25, 2025, whichever is earlier.

4. Cangene commits to (b) (4)

(b) (4)

Cangene will submit the final validation report as a Postmarketing Study Commitment – Final Study Report by March 16, 2016.

5. Cangene commits to developing (b) (4) submitted as a CBE-30 by March 16, 2016, and will be applicable to any new lots of Anthrax Immune Globulin (Human) manufactured after you are notified that this PMC is fulfilled.

6. Cangene commits t (b) (4) Postmarketing Study Commitment – Interim Study Report by September 16, 2015. If the initial assessment is supportive, a complete assessment that includes supportive stability data will be submitted as a Postmarketing Study Commitment – Final Study Report by March 16, 2016.

7. Cangene commits to (b) (4) will be submitted as a CBE-30 to FDA by May 16, 2015.

8. Cangene commits to (b) (4) will be submitted as a CBE by March 25, 2016.

9. Cangene commits to submitting a request for exemptions or alternatives to labeling requirements for biological products held by the Strategic National Stockpile per 21 CFR 610.68. This request will include specific lot numbers, the labeling provisions that are the subject of the exemption or alternative request, an explanation why compliance with the labeling regulations could impact the safety, effectiveness, or availability of Anthrax

Immune Globulin (Human), a description of proposed safeguards to ensure the labeling of the product conveys adequate information for the safe and effective use of the product, and a draft of the proposed labeling. Cangene will submit this information as a CBE-30 by April 25, 2015.

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125562. Please refer to the sequential number for each commitment and the submission number as shown in this letter.

Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Commitment – Status Update**
- **Postmarketing Study Commitment – Final Study Report**
- **Supplement Contains Postmarketing Study 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 Study 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-506B PMC; and,
- summarize any data collected or issues with fulfilling the non-506B PMC.

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

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

Enclosure:
Final Approved Draft Labeling