DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administrati
1401 Rockville Pike
Rockville, MD 20852-1448

December 20, 2006

Our Reference: CRMTS # 5932
Type C meeting for Lyophilized, Single-Donor Human Fresh-Frozen Plasma (LHP)

Department of the Army
Attention: Robert Miller, Ph.D., RAC
1430 Veterans Drive
Fort Detrick, Maryland 21702-5009

Dear Dr Miller:

We have reviewed your submission dated October 31, 2006, containing a Type C meeting information package. In a telephone call from Ms. Sharyn Orton and Mark Shields of this office on November 29, 2006, Richard Potter of your office was informed that in lieu of the face-to-face meeting you requested, FDA would be responding to your questions in a letter. You have the option of contacting us again, after reviewing our responses, for a Pre IND meeting.

FDA's responses to the questions submitted in the pre-read material are as follows:

Questions from Sponsor:

Question 1: Will LHP *in vitro* tests demonstrating factor activity levels within the normal range for FFP and hemovigilance/biovigilance data (both active and passive) demonstrating comparable safety relative to FFP be sufficient to support submission of a BLA for LHP?

FDA Response: No. Using *in vitro* tests to demonstrate factor activity to be within normal range of FFP and a hemovigilance/biovigilance program to demonstrate safety profile comparable to FFP will not be sufficient to support licensure for LHP because of the following reasons:

- Lyophilization is considered to have a substantial potential to adversely affect the safety and efficacy of plasma for transfusion.
- Protein S activity may be adversely affected by the manufacturing process.
- From our experience with PLAS SD (Vitex), a small imbalance between the coagulants and anticoagulants (especially in situations where massive transfusions are needed) can precipitate Adverse Events especially thromboembolic events.
- Keeping in line with FDA's current practice on this type of product, clinical study (ies) to evaluate safety and efficacy of the product will be required. This study could be conducted in a patient population requiring massive plasma exchange, for example, in Thrombocytopenic Thrombotic Purpura (TTP).

Question 2: isolation between individual units

FDA Response:

precautions taken to prevent contamination or cross contamination. Please indicate in which rooms the plasma will be introduced and the manufacturing steps that will take place in these rooms. An explanation should be given as to whether plasma will be introduced on a campaign basis or concurrently during production

(dedicated vs. multi-use equipment should be delineated for each process step) and a description of the in-process controls performed to prevent or to identify contamination or cross-contamination should be provided.

Question 3: manufacturing process and quality controls

FDA Response:

Contamination Control

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Lyophilization

- In the "Meeting Objectives" (page 19), CBER is asked to determine whether lyophilization of plasma is a "minimal modification" as compared to fresh frozen plasma. From a manufacturing perspective, lyophilization is a critical manufacturing step requiring a validation effort that is arguably more than "minimal." Subtle variations during the lyophilization process can significantly impact product characteristics. Thus, CBER expects a high level of control during the lyophilization process, which should be demonstrated by a thorough validation of the process.

- Please note that the validation of the lyophilization process is product specific, with allowances for limited bracketing upon adequate assurance that the products being bracketed are suitably represented by the bracketing products.

- CBER expects that temperature control is demonstrated during validation by performing empty chamber mapping studies. These studies should show temperature consistency throughout the chamber during the operation of the freeze dryer.

- Prospective validation studies using actual product should be performed. These studies should include product sampling and testing from locations on all shelves (both center and edges). Also, temperature control within the shelves and between shelves for a loaded chamber (i.e. product) should be demonstrated during this validation.

- There can be differences in product attributes depending on where in the chamber the sample was located.

- Please define all soak temperatures and ramp rates for all segments of the lyophilization cycle. What temperatures set-points will be used during all segments of the process? This would likely be determined during the development process. It may not be a desirable to simply use an existing cycle from another product, as the lyophilization process may affect this product differently. What is driving the cycle?

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- Is there a plan for testing for: reconstitution time, moisture content, pH and cake appearance of the lyophilized product? Typically, these tests should be performed during the validation on each shelf (middle and four corners).

- Please include the cleaning procedure for the Freeze Dryer?

- Please define the order in which one will load the freeze dryer shelves (i.e. top to bottom)?

- Please note that in addition to time, pressure and temperature are also considered critical attributes that must be controlled during the lyophilization process.

Media Fills

- media fills will be executed in accordance with ISO 13408. CBER recommends that manufactures follow FDA's Guidance for Industry "Sterile Drug Products Produced by Aseptic Process – Current Good Manufacturing Practices."

- the media fill procedures will include pulling a partial vacuum in the lyophilizer to simulate the aerodynamics during lyophilization and clarify the type of gas that one would use to overlay the media.

- all bottles should be filled with media.
  Typically, CBER expects three consecutive media fills.

Water System

- Please define the type of water used in the manufacturing process, what it is used for, and clarify if monitoring includes conductivity and Total Organic Carbon (TOC).

Product Specifications

- For a lyophilized product, CBER expects product specifications to include moisture content, reconstitution time, and cake appearance.

Question 4: Does CBER have any other concerns or suggestions regarding the submission of a BLA for LHP?

FDA Response:

- In the US, a plasma product prepared from Whole Blood is not labeled as single donor plasma. Single donor plasma is collected by apheresis.

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- The products are type specific individual units. There is no information on whether the lyophilization process alters antibodies of the ABO, Rh, non RH systems, leukocyte or granulocyte antibodies, in ways that would change in-vitro reactivity that may affect testing, or in-vivo reactivity that could produce more reactions in recipients.

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Please refer to the following guidance documents for additional information:

Guidance for Industry: For the Submission of Chemistry, Manufacturing, and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h, "Application to Market a New Drug, Biologic or an Antibiotic drug for Human Use."

Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products, Animal Plasma or Serum-Derived Products.

If you have any questions, please contact Mr. Mark Shields of this office at (301) 827-6173.

Sincerely yours,

B Golding

Basil Golding M.D.
Director
Division of Hematology
Office of Blood Research and Review
Center for Biologics
Evaluation and Research