December 18, 2014 Approval Letter - INTERCEPT Blood System for Platelets

December 18, 2014

Cerus Corporation
Attn: Ms. Carol M. Moore
2550 Stanwell Drive
Concord, CA 94520

APPROVAL ORDER

Re: PMA BP140143
INTERCEPT® Blood System for Platelets
Filed: July 1, 2014
Amended: July 14, 2014; August 4, 2014; August 27, 2014; September 15, 2014;
September 16, 2014; September 18, 2014; September 19, 2014;
September 24, 2014; September 25, 2014; September 26, 2014;
September 29, 2014; October 2, 2014; October 6, 2014;
October 14, 2014; October 22, 2014; October 26, 2014;
October 31, 2014; November 12, 2014; November 13, 2014;
November 17, 2014; November 18, 2014; November 19, 2014;
November 23, 2014; November 28, 2014; December 4, 2014;
December 9, 2014; December 10, 2014; December 15, 2014;
December 17, 2014; and December 18, 2014
Procode: PJF

Dear Ms. Moore:

The Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) completed its review of your premarket approval application (PMA) for the INTERCEPT® Blood System for Platelets. This device is intended to be used for *ex vivo* preparation of apheresis platelet components in order to reduce the risk of transfusion-transmitted infection (TTI) including sepsis, and to potentially reduce the risk of transfusion-associated graft versus host disease (TA-GVHD).

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). FDA has determined that this restriction on sale and distribution is necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84(b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have

been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, **http://www.fda.gov/udi (http://www.fda.gov/udi)**.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, you must provide the following data in post-approval study reports (PAS). Two (2) copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below.

A post-approval active hemovigilance study, CLI-HV 00112, will be conducted to evaluate the incidence of acute lung injury, with an emphasis on ARDS. This study is a prospective, open-label, multi-center, non-randomized, non-inferiority phase 4 surveillance study following transfusion of INTERCEPT processed platelets.

The primary outcome measure is the proportion of patients requiring treatment-emergent assisted mechanical ventilation during the study observation period. Assisted mechanical ventilation is selected as the primary outcome as it provides an objective measure of severe, clinically significant pulmonary injury. Additionally, the study will characterize the frequency of transfusion associated AEs and SAEs [including acute respiratory distress syndrome (ARDS) and clinically serious pulmonary AEs (CSPAEs)] and transfusion reactions (TR) in patients receiving at least one study platelet component (PC) transfusion. ARDS will be defined using the Berlin criteria. ARDS will be classified as related to platelet transfusion or as related to concurrent clinical conditions associated with ARDS in patients receiving platelet transfusion support. The patient population will be hematology-oncology patients, including those undergoing hematopoietic stem cell transplant (HSCT), expected to require one or more PC transfusions. Patients will be assessed for the primary outcome measure for up to 21 days of platelet transfusion support.

The study will be powered on the primary endpoint of treatment-emergent assisted ventilation [administered by intubation or tight fitting mask with positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥ 5 cm H2O]. The study is designed to use a cohort-sequential design with a comparative Control group supported with conventional PCs prior to implementation of INTERCEPT processed platelets in centers likely to adopt the Intercept Blood System for Platelets technology. Patients will be stratified by type of primary disease therapy (autologous HSCT, allogeneic HSCT, cord blood HSCT, and chemotherapy). The study will be conducted in two phases: 1) the control phase during which study patients will receive only conventional platelet components; and 2) the INTERCEPT phase during which patients will receive only INTERCEPT processed platelet components. For both phases, patients will be supported with study PC transfusions for a maximum of 21 days or until they become platelet independent. Patients are considered to have achieved platelet independence if more than 5 days elapse after exposure to a study PC transfusion. When a patient achieves platelet independence, the patient will have completed the study PC transfusion period (even if they subsequently resume another cycle of platelet support). Patients who have achieved at least 14 days of platelet independence after his/her first Control phase may be enrolled into the INTERCEPT phase.

A minimum of 1,466 patients per cohort period will be enrolled, which will provide approximately 90% power at one-sided alpha level of 0.025 to reject the null hypothesis of inferiority for the primary endpoint. For the primary endpoint, the following statistical hypotheses will be used:

H_0 (null hypothesis): p_Test - p_Control ≥ 0.023 vs.
H_1 (alternative hypothesis): p_Test - p_Control < 0.023,

where p_Test and p_Control are the proportion of patients requiring treatment-emergent assisted ventilation during the study observation period for the Test and Control groups, respectively. The non-inferiority test will be assessed by comparing the upper bound of the two-sided 95% exact confidence interval for the treatment difference (Test Control) in the proportions with the non inferiority margin of 0.023.

The proportions of patients with any ARDS by the Berlin criteria, any CSPAE, any AE, any TR, and any SAE will also be compared between treatment groups using the two-sided Fisher's exact test with a significance level of 0.05.

The median time to assisted ventilation from the first study PC transfusion within each study period will be estimated using the Kaplan-Meier method, and the treatment difference will be explored by the log-rank test.

Baseline data on primary disease (e.g., types of HSCT received) will be considered as covariates for association analysis.

The proportion of INTERCEPT PC containing platelet doses ≥ 3.0×10^{11} platelets will be summarized. Patient demographics, exposure to study PCs, and primary indication for transfusion will be summarized.

FDA would like to remind you that you are asked to submit a separate PAS Progress Report every six months until the completion of the study. The report should be clearly identified as "Post-approval Study Report." Two copies of the study identified as PMS Post Approval Study Report and bearing the applicable PMA reference number should be submitted to the address below. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA order" **http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm)**.

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study. Your PMA supplement should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (**www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm)**).

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (**www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm)**).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or
2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at **www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm (http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm)**.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at **www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm (http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm)**.

CBER does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CBER will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CBER Internet HomePage located at: **http://www.fda.gov/BiologicsBloodVaccines/BloodBlood-Products/ApprovedProducts/PremarketApprovalsPMAs/ucm089793.htm (http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm089793.htm)**. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law. You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

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

If you have any questions concerning this approval order, please contact Sonday L. Kelly, MS, RAC, at (240) 402-8410.

Sincerely,

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

Enclosure

Resources for You

- **INTERCEPT Blood System for Platelets (/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm427488.htm)**

More in Premarket Approvals (PMAs)
(/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/default.htm)