

QUESTIONS AND ANSWERS ABOUT PATHOGEN-REDUCED APHERESIS PLATELET COMPONENTS

Prepared by the AABB Pathogen Inactivation Technology Review Work Group

The Food and Drug Administration (FDA) has approved pathogen inactivation (PI) technologies that can be employed as an additional safety measure to help maintain a safe blood supply. The FDA has approved the INTERCEPT Blood System (Cerus Corp, Concord, CA) for pathogen reduction of 1) apheresis platelets stored in plasma and platelet additive solution (PAS) and 2) plasma. The FDA has also approved an additional pathogen-reduced plasma product, Octaplas (Octapharma, Vienna, Austria) that uses a solvent/detergent method. This document focuses solely on pathogen-reduced platelets treated using the INTERCEPT Blood System method.

What is pathogen reduction or pathogen inactivation?

PI is the process of treating the blood component soon after collection in order to inactivate any remaining infectious agents. Although the technology is termed pathogen inactivation, the components themselves are referred to as being pathogen reduced. The INTERCEPT method to produce pathogen-reduced platelets uses a chemical agent (amotosalen) that is activated by ultraviolet A (UVA) light to bind nucleic acids so that DNA cannot replicate and thus the cell cannot replicate. Because of the general nature of the inactivation technology, the process is effective against many infectious agents, including viruses, bacteria, parasites, and protozoa. The extent of the inactivation, and thus the effectiveness to prevent transfusion-transmitted infections, varies among different microbes. Red cells and platelets do not have nucleic acids and do not replicate. Lymphocytes do have nucleic acids; therefore, their proliferation is prevented by PI treatment.

What are the benefits of PI technology to patients?

The use of the technology may be expected to 1) materially reduce the risk of transfusion-transmitted infections for patients, 2) eliminate the need for serologic testing for cytomegalovirus (CMV) and production of CMV-reduced-risk components, and 3) eliminate the need for irradiation to prevent transfusion-associated graft-vs-host disease (TA-GVHD). The technology has been shown to inactivate meaningful titers of key viruses including human immunodeficiency virus, bacteria known to contaminate platelets, and parasites including those that cause malaria, babesiosis, and Chagas disease. In recent guidance documents, the FDA has indicated that the technology may be used to protect recipients from bacterial contamination and Zika virus infection. European studies have shown that there have been no cases of bacterial sepsis among patients receiving INTERCEPT platelets. INTERCEPT platelet components may be stored in plasma or PAS. PAS storage has been shown to reduce the frequency of allergic reactions among platelet recipients because there is 65% less plasma in the transfused component.

What should I expect from pathogen-reduced platelets?

A platelet component retains its original color and appearance after being treated using the INTERCEPT method. However, platelets stored in PAS have a lighter color than those stored in plasma. The FDA has approved a 5-day shelf life for INTERCEPT platelet components.

Summary of clinical evidence for efficacy of pathogen-reduced platelets: Evidence of the clinical efficacy of pathogen-reduced platelets comes from published studies and from European hemovigilance data from two countries in which universal pathogen reduction for platelets has been adopted (Belgium and Switzerland) and one country (France) in which universal pathogen reduction has been adopted at one regional blood center. A Cochrane review published in 2013 analyzed the results of 10 trials comparing pathogen-reduced platelets with standard platelets in hematology/oncology and stem cell transplant patients given prophylactic platelet transfusions to prevent bleeding. Nine trials assessed INTERCEPT technology in 1422 total participants, of whom 675 received INTERCEPT platelet transfusions.

Mortality and bleeding: The Cochrane meta-analysis demonstrated no differences in mortality, clinically significant bleeding, or severe bleeding between patient groups receiving INTERCEPT platelets and those receiving standard platelets. The outcome of “any bleeding” (ie, bleeding that includes clinically insignificant bleeding) was statistically different when analyzed using a fixed-effect model (favoring standard platelets) but was not statistically different between treatment arms when analyzed using a random-effect model.

The Italian Platelet Technology Assessment Study (IPTAS) was not included in the Cochrane review. In this randomized controlled trial, there was no significant difference in absolute risk of grade ≥ 2 bleeding (22.0% INTERCEPT vs 15.9% standard platelets, $p=0.16$) or in mortality. Other studies of PI for platelets are ongoing.

Corrected count increments and dosage: The Cochrane review showed that corrected count increments (CCIs) at 1 hour and 24 hours were statistically significantly lower after INTERCEPT platelet transfusions compared to standard platelets. The relative risk of platelet refractoriness (defined as low CCIs in two successive transfusions in four studies but defined as also including the presence of platelet antibodies in another study) was 2.74-fold higher with INTERCEPT platelets compared to standard platelets. Patients receiving INTERCEPT platelets required 7% more platelet transfusions and the transfusion interval between multiple INTERCEPT platelet transfusions was shorter than with standard platelets.

Reports of septic transfusion reactions from platelet transfusion: In Switzerland, no cases of sepsis due to INTERCEPT platelet transfusions have been reported to the Swiss hemovigilance system, during 130,800 pathogen-reduced platelet transfusions from 2011-2014. In Belgium, more than 150,000 pathogen-reduced platelet products have been transfused since 2009. None of the transfusions resulted in transfusion-transmitted bacterial infections (TTBIs). For comparison, in the same period, four TTBIs were reported in approximately 186,000 standard platelet transfusions in the Flanders region of Belgium. In France in the 9-year interval from 2007-2015, there were no reported TTBI cases in the region that transfused only INTERCEPT platelets. In contrast, there were 47 cases, including nine fatalities, in parts of France that transfused standard platelets.

Reports of transfusion-related acute lung injury: According to the Swissmedic Hemovigilance reporting, the incidence of transfusion-related acute lung injury was 1:30,000 after transfusion of standard platelets, compared with 1:24,000 after transfusion with INTERCEPT platelets—essentially no difference.

What are the theoretical risks and limitations of this technology to patients?

Psoralen toxicity: In order for platelets to undergo the INTERCEPT method, a psoralen (amotosalen, previously called S-59) is added in conjunction with UVA light exposure. Although the amotosalen is mostly removed using a compound adsorption device, this creates concern for toxicity in transfusion recipients. However, in-vitro data, animal data, and European hemovigilance data show that the dose of amotosalen in INTERCEPT components is safe. The INTERCEPT method is contraindicated for preparation of platelet components intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens.

Acute respiratory distress syndrome: A warning/precaution in the INTERCEPT package insert notes the risk of acute respiratory distress syndrome, which occurred in a randomized trial involving adults. However, a published reanalysis of the data, sponsored by Cerus, did not confirm this association and hemovigilance systems have not reported an increased risk. A more rigorous evaluation by an ongoing Phase IV postmarketing trial in the United States is actively evaluating this risk.

Di(2-ethylhexyl)phthalate exposure: The risks associated with di(2-ethylhexyl)phthalate (DEHP) released into the blood components must be weighed against the benefits of therapeutic transfusion. The FDA reviewed issues related to DEHP and released the following notices in 2001 "[Safety Assessment of Di\(2-ethylhexyl\)phthalate \(DEHP\) Released from PVC Medical Devices](#)" and 2002 [FDA Public Health Notification: PVC Devices Containing the Plasticizer DEHP](#).

Phototherapy: The INTERCEPT method is contraindicated for preparation of platelet components intended for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

How is this component different from the platelet components already in use?

A wide array of platelet components is currently available for use in the United States, including apheresis platelets stored in plasma, apheresis platelets stored in PAS, whole-blood-derived platelets, and prestorage pooled whole-blood-derived platelets. INTERCEPT apheresis platelets can be stored in plasma or PAS. The components are all approved by the FDA to deliver a therapeutic platelet dose.

Are there alternative safety measures to achieve similar goals?

Although there are no other broad-spectrum alternatives to pathogen-reduced platelets, there are targeted alternatives for specific safety threats, including direct testing for infectious agents. All infectious disease screening tests on donor blood with the exception of bacterial culturing are performed in the same fashion for apheresis platelet donors whether or not the component is pathogen reduced. Other measures that achieve safety objectives similar to PI include serologic testing and/or leukocyte reduction to mitigate transfusion-transmitted CMV and gamma irradiation to prevent TA-GVHD. CMV testing and gamma irradiation can be replaced by PI technology.

Bacteria: Primary bacteria testing of platelets, currently performed by culture system, is the initial testing to detect the presence of bacterial contamination. The two culture systems for primary testing approved by the FDA for use in the United States are BacT/ALERT (bioMerieux, Marcy l’Etoile, France) and Enhanced Bacteria Detection System (eBDS; Pall Corporation, Port Washington, NY). The FDA has also introduced the terminology of secondary bacterial testing. Secondary testing of platelets refers to the use of any additional test to detect the presence of bacterial contamination in a unit that previously showed no bacterial contamination on initial testing. Secondary testing can be conducted using a culture-based method or a rapid bacteria detection device (point-of-release test). Current FDA-approved rapid tests are the Platelet PGD Test System (Verax Biomedical, Marlborough, MA), which has also received an additional “safety measure” claim from the FDA, and BacTx Bacterial Detection Kit for Platelets (Immunetics, Boston, MA). Platelets that have been pathogen reduced do not need to be tested for bacterial contamination by either primary or secondary testing.

Zika virus: The February 2016 FDA guidance document regarding the risk of Zika virus in donated blood recommended that in areas with active Zika virus transmission, 1) whole blood and blood components for transfusion be obtained from areas of the United States without active transmission, or 2) blood establishments may continue collecting and preparing platelets and plasma if an FDA-approved pathogen reduction device is in use, or 3) all blood components (including Red Blood Cells) may be used if an FDA-licensed blood screening test for Zika is in use. In addition, the FDA noted that use of an investigational donor screening test under an investigational new drug application may be permitted in situations where approved technologies are unavailable. The August 2016 FDA guidance document on this subject recommends that all blood products be tested for Zika virus using an investigational nucleic acid amplification test, or when available, a licensed test, and continues to allow use of pathogen-reduced platelets as an alternative to testing.

References

Butler C, Doree C, Estcourt LJ, et al. Pathogen-reduced platelets for the prevention of bleeding. *Cochrane Database Syst Rev* 2013;(3):CD009072.

Cerus Corporation. INTERCEPT Blood System for platelets—small volume processing set (package insert). Concord, CA: Cerus, 2016. [Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/UCM427512.pdf>.]

Corash L, Benjamin RJ. The role of hemovigilance and postmarketing studies when introducing innovation into transfusion medicine practice: The amotosalen-ultraviolet A pathogen reduction treatment model. *Transfusion* 2016;56(Suppl):S29-38.

Food and Drug Administration. Guidance for industry: Recommendations for donor screening, deferral, and product management to reduce the risk of transfusion transmission of Zika virus. Silver Spring, MD: CBER Office of Communication and Outreach Development, 2016.

[Available at:

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM486360.pdf>.]

Food and Drug Administration. Guidance for industry: Revised recommendations for reducing the risk of Zika virus transmission by blood and blood components. Silver Spring, MD: CBER Office of Communication and Outreach Development, 2016. [Available at:

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM518213.pdf>.]

Food and Drug Administration. Draft guidance for industry: Bacterial risk control strategies for blood collection establishments and transfusion services to enhance the safety and availability of platelets for transfusion. Silver Spring, MD: CBER Office of Communication and Outreach Development, 2016. [Available at:

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM425952.pdf>.]

Food and Drug Administration. Safety assessment of di(2-ethylhexyl)phthalate (DEHP) released from PVC medical devices. [Available at:

<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080457.pdf>]

Food and Drug Administration. Public health notification: PVC devices containing the plasticizer DEHP. [Available at: <https://wayback.archive-it.org/7993/20170111182403/http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062182.htm>]

Rebulla P, Grazzini G, Liunbruno GM, et al. Pathogen inactivated platelets and prevention of immunological adverse reactions: The Italian Platelet Technology Assessment Study (IPTAS). *Blood Transfus* 2009;7(Suppl 1):s19-s21. DOI 10.2450/2009.0013-09.

Swissmedic. Haemovigilance annual report 2015. Berne, Switzerland: Swissmedic, 2015.

[Available at:

<https://www.swissmedic.ch/marktueberwachung/00138/00188/index.html?lang=de.>]

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