Frequently Asked Questions (FAQs) related to Apheresis Platelet Products Offered by Versiti to Meet the FDA Bacterial Mitigation Guidance

As of 4/1/2021

KEY POINTS: Use of Pathogen Reduced (PR) & Large Volume Delayed Sampling (LVDS) Platelets

- PR platelet transfusions are as effective as conventional platelets with respect to safety and prevention of bleeding.
- Excluding septic reactions, the incidence or type of transfusion-related adverse events in patients receiving PR platelets is no different than in those receiving conventional platelets.
- Pathogen reduction technology is equally effective as irradiation in preventing proliferation of T-lymphocytes. For patients at risk for TA-GVHD, PR platelets do not require irradiation; however, LVDS platelets do need to be irradiated.
- PR platelets are considered equivalent to CMV seronegative platelets and testing for CMV is not required. LVDS platelets may be ordered CMV-seronegative.
- If an LVDS platelet is washed, plasma-reduced, or becomes an "open" system then the "Bacterial Monitoring/Testing" attribute value should be removed from the labeling; product should be relabeled with an ISBT code that indicates an "open" system integrity.

GENERAL INFORMATION

Why is the FDA recommending these bacterial mitigation changes to platelet products?

- Despite mitigation measures, bacterial contamination and septic reactions remain a significant risk with platelet transfusions. Since 2004, prevention measures at Versiti have included a single culture (aerobic only) performed no sooner than 24 hours after collection of the apheresis platelet with a minimum 12 hour-incubation of the culture prior to labeling and release for distribution to hospitals.[1]
- Based on available scientific evidence and implications on operational implementation, the FDA has recommended several strategies utilizing FDA-approved or cleared devices to further reduce the risk of bacterial contamination and septic transfusion reactions. Pathogen reduction technology (PRT) and large volume delayed sampling (LVDS) are two of these options.
- Based on customer feedback Versiti has implemented both PRT and LVDS as strategies to mitigate bacterial contamination in platelets. PR platelets supplied by Versiti will be suspended in 100% plasma. See ***Apheresis Platelet Products Offered by Versiti: A Side by Side Comparison*** table for further details and comparison of these platelet products.
- Data from large hemovigilance programs in Europe and UK shows the incidence of septic transfusion reaction is significantly lower in pathogen reduced (PR) platelets and LVDS platelets compared to conventionally screened platelets.[2]

PATHOGEN REDUCED (PR) PLATELETS

What is the clinical indication for use of pathogen reduced (PR) platelets in adult patients?

- PR platelets can be used for all patients according to the standard of care for platelet transfusion indications.
- PR platelets may be used in conjunction with other available platelets (e.g. conventional or large volume delayed sampling), as needed.

What is the clinical efficacy of pathogen reduced (PR) platelets in the adult patient?

- Most trials comparing PR platelets to conventional platelets involved hematology/oncology patients who were thrombocytopenic due to their disease or treatment. A meta-analysis of 12 trials[3] in this patient population found that PR platelet transfusions were as effective as conventional platelets with respect to safety and prevention of bleeding. In several of the studies, patients receiving PR platelets had a lower platelet recovery posttransfusion with a slightly shorter interval between transfusions (about 0.5 days less), and an increase in the number of platelet transfusions required.[3,4]
- Post-market retrospective studies have not documented increased platelet utilization nor has RBC utilization differed supporting the hemostatic effectiveness of PR platelets. While platelet utilization at one center[5] was statistically higher following policy change to PR platelets (1.78 vs 1.45 units per patient), the total increase in platelet transfusion burden was clinically small. More importantly, during the study period at this institution, five septic transfusion reactions were associated with conventional platelets but none with PR platelets.
- While PR platelets have been primarily studied in thrombocytopenic hematology/oncology patients, there is no reason to believe that PR platelets would not provide similar clinical benefit in other patient populations. A retrospective cohort analysis of 306 patients who had massive transfusion in the setting of trauma, liver transplant, and cardiovascular surgery found that introduction of PR platelets did not adversely affect clinical outcomes measured by blood product usage, in-hospital mortality, and length of stay.[6]
- The choice of products for transfusion must balance efficacy and safety. While there may be a risk of lower posttransfusion platelet counts and need for additional transfusions in hematology/oncology patients when using PR platelets, this must be weighed against the potential risk for bacterial contamination and sepsis in this vulnerable patient population.

Are PR platelets considered equivalent to irradiated platelets?

- Pathogen reduction technology involving amotosalen plus UV-A light treatment inactivates DNA replication in cells, including the DNA in donor T-lymphocytes that may be present in the platelet bag.
- Pathogen reduction is as equally effective as irradiation in preventing proliferation of donor T-lymphocytes for prevention of transfusion-associated graft-versus-host-disease (TA-GVHD).[6] Thus, pathogen reduced platelets do not require irradiation for patients at risk for TA-GVHD.
- In addition, AABB Standards (BBTS Std 5.19.14.1 for prevention of TA-GVHD) considers the FDA-approved pathogen reduction technology equivalent to irradiation.[7]

PR platelets distributed by Versiti will not be irradiated. For hospital platelet orders specifying "pathogen-reduced" and "irradiated", PR platelets will be selected to fill the order.

Are PR platelets considered equivalent to CMV-seronegative platelets?

- Pathogen reduction technology (PRT) involving amotosalen plus UV-A light treatment inactivates a broad range of viral, bacterial, and protozoan pathogens, including CMV. By inactivating both cell-associated and cell-free CMV, PR is highly effective in prevention of transfusion-transmitted CMV infection.[8] Thus, PR platelets are considered equivalent to CMV seronegative platelets and testing for CMV is not required.
- In addition, the *Circular of Information for Blood and Blood Components* states that for at-risk recipients the risk of CMV transmission from cellular blood products can be reduced by transfusing CMV seronegative or leukocyte-reduced or pathogen-reduced components.[9]

PR platelets distributed by Versiti will not be preferentially selected for CMV antibody testing.* For hospital platelet orders specifying "pathogen-reduced" and "CMV-negative", PR platelets without respect to "CMV serostatus" will be selected to fill the order.

**Note: At Versiti, testing for CMV antibody on a donor may be performed prior to designation of that donor's platelet product for further manufacturing by PRT. In these situations and when testing is negative, the PR platelet product may be labeled as "CMV seronegative".*

What is the risk of transfusion reactions with PR platelets compared to conventional platelets?

- Excluding septic reactions, no difference was found in the incidence or type of transfusion-related adverse events in adult or pediatric patients receiving PR platelets versus those receiving conventional platelets.[4,10]
- As part of a 7-year hemovigilance surveillance program conducted in Europe where over 19,000 PR-platelets have been transfused, the rate of acute transfusion reactions and serious adverse events with PR platelets was similar to past rates with conventional platelets. There were no cases of transfusion-related acute lung injury, transfusion-associated graft-versus-host disease, or transfusion transmitted infections.[10]
- In a retrospective review of platelet transfusions occurring from November 2016 to February 2019 at one US medical center, no difference in rate or type of transfusion reactions was seen in adult or pediatric patients receiving PR platelets (n=14,067) compared to conventional platelets (n=9772). Notably, there were 5 cases of septic transfusion reactions in the adult patients receiving conventional platelets while no septic transfusion reactions followed PR platelet transfusion.[4,11]
- In the SPRINT study (randomized controlled trial conducted for licensing of PR platelets in the US), an increase in incidence of acute respiratory distress syndrome (ARDS) was initially reported in patients receiving PR platelets (n=5/318) compared to conventional platelets (n=0/318).[12] However, after reanalysis of the SPRINT data no difference in incidence of ARDS or acute lung injury (ALI) was found. The discrepancy was believed to be due to differences in criteria used for ALI diagnosis across the study sites.[13] In addition, international hemovigilance programs and subsequent retrospective data from academic centers involving over 33,000 PR platelet transfusions have not identified an increase in frequency of adverse respiratory events with PR platelets.[4,10,11]

Are there any contraindications to pathogen reduced (PR) platelets for adult patients?

- Per the package insert,[14] patients with a history of hypersensitivity reaction to amotosalen or other psoralens should not receive pathogen reduced (psoralen-treated) platelets.
    - "Amotosalen" is the name of the specific psoralen used in the INTERCEPT® Blood System treatment process. Psolarens are chemicals found in certain plants that absorb UV-A light and can increase the skin's sensitivity to light.
- The risk of a hypersensitivity reaction with the use of PR platelets appears quite low because of the following:
    - Psoralen treated products have been in routine use in patients in Europe (15+ years) and USA (3+ years) with over 5 million psoralen treated components administered with **no hypersensitivity reaction to psoralen reported to date.**[4,10,14]
    - Psoralens are present in a wide variety of foods – citrus fruits, celery, carrots, figs. More psoralen is consumed in one stalk of celery than is used to psoralen-treat one unit of apheresis platelet.[15]
    - The majority of psoralen is removed from the platelet bag before the unit is labeled and made available for distribution to the hospital transfusion service.[14]
- The manufacturer's warning of PR platelet intended for neonatal patients treated with phototherapy devices is addressed in the *FAQs: Pathogen Reduced Apheresis Platelets & Use in Pediatric and Neonatal Patients*.

Are there any potential toxicities of amotosalen (psoralen used in preparation of pathogen reduced platelets)?

- Psoralens are present in a wide variety of foods – citrus fruits, celery, carrots, figs. More psoralen is consumed in one stalk of celery than used to psoralen-treat one unit of platelets.[15]
- In animal studies, only amotosalen doses ≥100,000-fold the amount in a single processed Intercept® pathogen reduced (PR)-platelet was shown to be harmful. Even when the animals received repeated daily amotosalen injections for 7-28 days with doses equivalent to 10,000-30,000-fold the potential amount in a 300 mL Intercept® PR-platelet unit, there was no evidence of toxicity.[14]

Are there any precautions or special handling for pathogen reduced (PR) platelets?

When handling PR platelet products, the following good laboratory practices may help to decrease any risk of bacterial contamination.[16] In fact, many of these practices would also apply to all platelet products.

- Ensure work surfaces are clean and disinfected to avoid contamination of the outside of the bag.
- Avoid pinching, friction, excessive pressure (e.g. stacking of bags) of the PR platelet during storage or transport to prevent risk of puncture or damage to the bag or ports.
- Always inspect the platelet containers for any leaks or damage during receipt, product selection, product issue and shipping.
- When using a pneumatic tube system for transport of PR platelets to patient care areas, these steps may avoid damage to the platelet:
    - Ensure carrier is padded and airtight and system is validated for delivery of blood products.
    - Place platelet inside sealed transport bag or pouch before placing in the carrier.
    - Ensure ports of the platelet bag are pointing away from the direction of travel.
    - Minimize the number of times the platelet is transported via pneumatic tube.
    - If the product must be folded to fit inside the carrier, fold at the bottom where INTERCEPT BLOOD SYSTEM embossing is and NOT at the ports.
- For more information on proper handling and/or storage of PR platelets refer to Cerus INTERCEPT® Blood System for Platelets: Handling Recommendations for Hospitals.

LARGE VOLUME DELAYED SAMPLING (LVDS) PLATELETS

What are Large Volume Delayed Sampling (LVDS) platelets?

- A LVDS platelet is an apheresis platelet from which both an aerobic and anaerobic culture (e.g. bioMerieux BACT/ALERT®) are obtained; and these cultures are taken at a **minimum of either 36 or 48 hours** after collection.
- LVDS does not indicate that the volume of the platelet product is larger than conventional apheresis platelets. The term refers to the amount of sample removed from the platelet product for bacterial testing (≥16 mL versus 8 mL). LVDS apheresis platelets manufactured by Versiti average 183-346 mL, which is comparable to the volume of conventional apheresis platelets (200-350mL).
- LVDS platelets are one option to meet the FDA Bacterial Mitigation Guidance.[1]

What is the efficacy of Large Volume Delayed Sampling (LVDS) platelets?

- The efficacy of LVDS platelets is comparable to conventional apheresis platelets.
- With LVDS platelets there is increased safety with respect to lower risk of transfusion-transmitted septic reactions and improved platelet inventory management.[17,18] At Canadian Blood Services after implementation of LVDS platelets, the rate of septic reactions associated with false-negative culture screening results decreased from approximately 1 in 100,000 to 1 in 350,000 for platelets with 7-day shelf life.[18]

Are there any limitations when performing component modifications with LVDS platelets?

Yes. There are labeling restrictions when an LVDS platelet undergoes component modification such as volume-reduction or washing. As per ICCBA guidelines[19], the product description on the label cannot contain a "Bacterial Monitoring/Testing" attribute in combination with any of the following: (1) washed modifier; (2) open system attribute; or (3) plasma reduced attribute.

- The "Bacterial Monitoring/Testing" attribute values and the "OPEN" system integrity attribute values contradict one another. "Bacterial Monitoring/Testing" indicates an extension of the expiration, whereas "Washed", "Open", and "Plasma Reduced" shorten the product's expiration date. Any of these three would conflict with the "Bacterial Monitoring/Testing" attribute within the same product description.
- If an LVDS platelet is washed, plasma reduced, or the product becomes an "open" system (i.e. spiked), then the "Bacterial Monitoring/Testing" attribute value would need to be omitted.
    - If you prepare such products at your facility, the product should be relabeled with a code that indicates an "OPEN" system integrity. For example:
      E3015 = Apheresis PLATELETS|ACD-A/XX/20-24C|Open|ResLeu:<5E6|Plasma reduced
      E3541 = Washed Apheresis PLATELETS|None/XX/20-24C|Open|Irradiated| ResLeu;<5E6
    - If an LVDS platelet is further washed or volume-reduced and distributed from Versiti, the 'final' product will be labeled with similar ISBT codes as when conventional platelets were used to prepare such products.

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