Advancing Transfusion and Cellular Therapies Worldwide

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To: AABB Members

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Karen Shoos Lipton, JD – Chief Executive Officer

Re: Information Concerning Platelet Additive Solutions (Updated table)

Summary

FDA recently approved the first platelet additive solution (PAS) for apheresis platelet storage in the United States (PAS-C; InterSol, Fenwal/Baxter, Lake Zurich, IL). The PAS replaces a portion of the plasma used when storing platelets. PAS platelets are leukocyte-reduced apheresis platelets that are stored in a mix of 65% PAS and 35% plasma, and can be stored up to 5 days at 20-24 C with continuous agitation. This first approved PAS may only be used with the AMICUS Separator System (Fenwal/Baxter, Lake Zurich, IL). Additional PASs are under development and may be approved by FDA for use in the United States in the foreseeable future. In this Association Bulletin, the following PASs, identified by ISBT Code Descriptor, are referenced: PAS-A = PlasmaLyte A (Fenwal/Baxter); PAS-B = T-Sol, PASII, or SSP (Fenwal/Baxter); PAS-C = PAS III or Intersol (Fenwal/Baxter); PAS-D = Composol (Fresenius); PAS-E = PAS IIIM or SSP+ (MacoPharma); and PAS-G = (No Trade Name) (Pall). The composition of these different PASs with their ISBT codes are presented in the table below.

Association Bulletins, which are approved for distribution by the AABB Board of Directors, may include announcements of standards or requirements for accreditation, recommendations on emerging trends or best practices, and/or pertinent information. This bulletin contains information, some of which supports existing standards requirements, to consider in determining whether to collect and transfuse apheresis platelets stored in PAS. Considerations include the following:

- Platelets stored in PAS appear to have equivalent efficacy with regard to the clinical outcome of bleeding, compared to platelets stored in plasma.
- The data on corrected count increments (CCI) are mixed. One recent study reported for PAS-C stored platelets showed no difference in CCI. However, two studies showed that

platelets stored in PAS-B (not available in the US) may result in smaller posttransfusion platelet count increases than platelets stored in plasma.
- Platelets stored in PAS have been demonstrated to have a lower risk for allergic transfusion reactions.
- Collection of platelets stored in PAS may permit collection of more blood products from the same donor during each apheresis donation because the reduced amount of plasma required for platelet storage results in more available plasma for collecting additional products.

Background regarding platelet additive solutions

PASs have been developed in order to increase platelet viability during storage, minimize the amount of plasma in platelet products, and make more plasma available for other needs. Multiple PASs have been developed and are in use throughout the world for both whole blood-derived and apheresis platelet products. The issue of the efficacy of platelets stored in PAS versus plasma has been evaluated in three randomized controlled trials, two with PAS-B and one with PAS-C. There were no demonstrated differences in bleeding outcomes in any of the three studies. The two studies conducted with PAS-B showed decreased CCI for the PAS-stored platelets compared to platelets stored in plasma, whereas the study of PAS-C-stored platelets showed no CCI difference. It is unknown if the different results in these studies are due to the somewhat different chemical compositions of PAS-B and PAS-C. More details about the results of the three studies are presented below.

The study with PAS-C[1] compared the use of platelets stored in PAS-C, platelets stored in plasma, and a third group of platelets stored in PAS-C and treated with the INTERCEPT pathogen reduction technology (PR-PAS-C) in 278 thrombocytopenic hematology/oncology patients. Clinical efficacy was not statistically different between platelets in PAS-C compared to plasma and there was no difference in CCI (1 hr: 15.3 ± 6.7 PAS-C versus 17.1 ± 7.3 plasma; 24 hours: 11.7 ± 7.6 PAS-C versus 12.5 ± 7.7 plasma), the interval between platelet transfusions, number of platelet transfusions, and number or severity of bleeding episodes.

The earliest study with PAS-B (which is not licensed in the US) by de Wildt-Eggen et al[2] compared PAS-B to plasma storage in 21 patients receiving intensive chemotherapy for hematologic malignancies. The 1- and 20-hour CCI for platelets stored in PAS-B were significantly lower compared to plasma (1 hr: 17.1 ± 6.6 PAS-B versus 20.7 ± 8.5 plasma, $p<.001$; 20 hours: 9.5 ± 8.0 PAS-B versus 11.5 ± 8.0 plasma, $p<.05$). A second PAS-B

study[3] compared platelets stored in PAS-B to plasma in 168 hematological malignancy patients. The 1-hour, but not the 24-hour, CCI for platelets stored in PAS-B was significantly lower compared to plasma (1 hr: 11.2 ± 6.4 PAS-B versus 13.9 ± 7.0 plasma, p=.004; 24 hours: 6.8 ± 6.4 PAS-B versus 8.4 ± 6.9 plasma, p=.09). The transfusion interval, number of transfusions per patient, and number and severity of bleeding complications did not differ between the two groups. In a multivariate analysis of transfusion failure, storage medium was not a significant factor.

A potential advantage of PAS-stored platelets is that, due to the decreased plasma volume, the incidence of transfusion reactions may be reduced. Three studies, all conducted with PAS-B stored platelets, have demonstrated an approximately 50% decrease in transfusion reaction rates for PAS-stored versus plasma-stored platelets. The first study[2] demonstrated a decrease in the incidence of transfusion reactions (PAS-B 56% of patients with reactions versus plasma 80% of patients with reactions; PAS-B 5% of transfusions resulting in reactions versus plasma 12% of transfusions resulting in reactions). This difference was particularly notable for allergic reactions. The second study[3] demonstrated a reduction in transfusion reactions between platelets stored in PAS-B and plasma (PAS-B 2.4% of transfusions versus plasma 5.5% of transfusions, p=.04). The third study[4] using hemovigilance data from France demonstrated a significant reduction in allergic reactions in platelets in PAS-B versus plasma (p<.05). However, one randomized controlled trial with PAS-C[1] did not demonstrate a decrease in transfusion reactions with the use of PAS-C compared to plasma-stored platelets (PAS-C 9% of patients versus plasma 11% of patients). In contrast, a previous study with pathogen reduced PAS-C-stored platelets showed a statistically significant decrease in transfusion reactions, presumably due to a decreased plasma transfusion volume rather than to the pathogen reduction treatment.[5] Furthermore, two large observational hemovigilance studies have documented low reaction rates with pathogen reduced PAS-C stored platelets.[6,7] In summary, the data suggest that platelets stored in PAS versus plasma may result in decreased transfusion reactions, particularly allergic reactions.

Theoretically, transfusion of platelets stored in PAS versus plasma could result in a lower incidence of other plasma-associated transfusion reactions, such as ABO hemolytic reactions and transfusion-related acute lung injury. To date, there are no published clinical or hemovigilance data to support these theoretical benefits.

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Possible actions for supplying and issuing platelets stored in platelet additive solutions

FOR BLOOD CENTERS

- When using PAS, SOPs for product collection must be modified, as specified in the manufacturer's instructions. The number of blood products collected from a single donor at each apheresis donation can be increased as per the manufacturer's instructions.
- PAS is currently only approved for a specified apheresis collection instrument (AMICUS) for leukoreduced apheresis platelets.
- With regard to bacterial detection methods, data have recently been published regarding use of BacT/ALERT with PAS-C stored platelets.[8] In addition, Section 2.2 of the AMICUS Operator's Manual, revision 3.2 states: "For blood centers using the BacT/ALERT Microbial Detection System, it should be noted that Fenwal has validated the use of this bacterial testing system. Fenwal has shown that it can be used with platelets stored in 65% InterSol / 35% plasma, when the current instructions for use of the BacT/ALERT Microbial Detection System are followed." There are no similar statements with regard to the use of other bacterial detection systems.
- ICCBBA, which manages, develops, and licenses ISBT 128, has recently added PAS to ISBT 128 product codes.[9] There are no other labeling requirements. P-Codes, product billing codes, are available.
- Implementation processes are similar to other apheresis components. The licensure process and requirements for PAS platelets are the same as for platelets stored in 100% plasma.
- PAS should not be directly infused into a patient; it should only be used to replace a proportion of the plasma in leukoreduced platelet products.

FOR TRANSFUSION SERVICES AND BLOOD CENTERS

- The platelet collection procedure and storage container is the same as for current apheresis platelets stored in plasma.
- Platelet counts and storage fluid volumes are not affected by PAS.
- Irradiation and volume-reduction can be performed as in platelets stored in plasma.
- Variation in color is expected. As with platelets in plasma, platelets in PAS may be lighter in color in some instances.
- Swirl can be detected.

FOR TRANSFUSION SERVICES

- Transfusion services that have policies to reduce the risk of hemolytic transfusion reactions due to ABO incompatibility by titering and/or volume reducing the product and/or limiting total volume of incompatible plasma transfused should review these

policies and possibly revise them because of the 65% less plasma in platelets stored in PAS compared to plasma.

- PAS does not contain mannitol or extra adenine or dextrose and therefore its use does not carry the same concerns as some red blood cell additive solutions for neonatal transfusions. However, a review of the contents of the new solutions should be performed with neonatologists to address any potential concerns with this product prior to use.
- Transfusion services may wish to discuss the use of platelets stored in PAS in their Transfusion Committees prior to implementing its use.
- For transfusion services that use aliquots of apheresis platelets (with sterile docking) for their pediatric patients, the minimum residual volume needed for platelets in PAS is the same volume as for platelets in plasma.
- The published coagulation factor values in platelet concentrates (in the AABB *Technical Manual*) will not be applicable to platelets in PAS, as there will be a lower value since the product contains one-third of the plasma volume.

Other

- The Circular of Information Task Force has provided FDA accepted language describing the PAS Platelet component that can be added to the *Circular of Information for the Use of Human Blood and Blood Components* until such time as the *Circular* is revised.
- The Blood Bank/Transfusion Services Standards Program Unit is currently evaluating this issue and is considering whether an interim standard regarding platelets stored in PAS in the Standards for Blood Banks and Transfusion Services, 27th Edition is necessary.

References

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Platelet additive solution (PAS) names and formulations are as described in the table below.

Table of Platelet Additive Solutions

New Name	Citrate	Phosphate	Acetate	Magnesium	Potassium	Gluconate	Glucose	Alternative Names	Previous *ISBT 128* Name
PAS	NS	NS	NS	NS	NS	NS	NS		Not named
PAS-A	X	X			X			PAS (1)	Not named
PAS-B	X		X					PAS-II, PAS-2, SSP, T-Sol	PASII

PAS-C	X	X	X					PASD-III, PAS-3, Intersol	PASIII
PAS-D	X		X	X	X	X		Composol PS	PAS IIIMgK (note, Composol PS should not have been called PASIIIMgK)
PAS-E	X	X	X	X	X			PASIIIM, SSP+	Not named
PAS-F			X	X	X	X		PlasmaLyte A, Isoplate	Not named
PAS-G	X	X	X	X	X		X		Not named

Source: Ringwald, J., Zimmerman, R., and Eckstein, R: The New Generation of Platelet Additive Solution for Storage at 22°C: Development and Current Experience, Transfusion Medicine Reviews, Vol 20, No 2 (April), 2006: pp 158-164.