Why Pathogen Reduction? – Use of Pathogen Reduced Platelets for Patient Safety and Sustainability

White Paper

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Executive Summary

FDA's final guidance on the mitigation of bacterial contamination in platelets, coupled with the current pandemic underscore the need for a proactive blood safety approach. INTERCEPT®-treated, pathogen reduced platelet components are the product of choice for many US institutions to enhance the safety and sustainability of platelets.

- **Safety and Efficacy**
  The safety and efficacy of INTERCEPT-treated, pathogen reduced platelet components are supported by several clinical trials as well as hemovigilance programs, all of which have demonstrated hemostatic efficacy, as well as no reported instances of inactivation failures leading to bacterial transfusion-transmitted infections, sepsis-related fatalities, or transfusion-associated graft versus host disease (TA-GVHD) to-date.
- **Platelet Sustainability/Pandemic Preparedness**
  Continued emergence of new pathogens makes it a challenge to ensure blood safety through testing alone. Pathogen reduction is a proactive approach that has helped sustain the local availability of platelets during outbreaks.
- **Economic/Operational Value and Optimal Shelf-Life**
  Pathogen reduction offers optimal operational and economic value with the potential to release transfusion-ready product sooner after collection, coupled with an ability to proactively inactivate bacteria as well as viruses, protozoa and T-cells.

This White Paper describes why pathogen reduced platelet components are the product of choice to mitigate transfusion transmission infectious risk due to bacteria and beyond.

Background

FDA's final guidance on the mitigation of bacterial contamination in platelets, coupled with the current pandemic underscore the need for a proactive blood safety approach. Despite the implementation of various safety measures, platelet components (PC) present the highest risk for transfusion-associated sepsis and related fatalities;[1-5] despite current safeguards, it's estimated that ~1 in 2,500 transfused components are contaminated with bacteria which often go undetected.[6] This prompted FDA to release a Final Guidance that requires implementation by blood centers and/or transfusion services by March 2021. The Guidance outlines several strategies to reduce the risk of bacterial transfusion transmission in platelet components, including pathogen reduction (PR) and various testing approaches.[1]

Most recently, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)/coronavirus disease 2019 (COVID-19) pandemic has highlighted concerns about health system infrastructure preparedness and the impact on blood product availability.[7] Blood shortages are anticipated as donations decrease due to cancelled donation appointments, donor deferrals, and usage increases with a surge in re-scheduled elective surgeries. Transfusion transmission of SARS-CoV-2 is considered theoretical at this time as no reported cases have been documented.[8] However, the rapid progression of the pandemic has further highlighted a need for the proactive management of potential transfusion transmitted infections (TTI) in general as transfusion-transmission would further threaten blood safety and availability.[9,10] Testing methodologies alone are not sufficient to mitigate TTI-related supply disruption from emerging infections. Testing often takes time for development and regulatory approval; furthermore, testing reagent supplies may be disrupted.

PR offers a proactive solution that addresses both FDA Guidance requirements for bacterial platelet contamination, as well as mitigation of TTI risks due to potential emerging pathogens. PR specifically

targets DNA and RNA to block the replication of viruses, bacteria, parasites and leukocytes, rendering them inactive.[11] The INTERCEPT® Blood System is the only FDA approved pathogen reduction system for platelet components.

Why Pathogen Reduction?

INTERCEPT-treated pathogen reduced platelet components are the platelet product of choice for many US institutions to enhance the safety and sustainability of platelets for transfusion, for all patient populations.

Safety and Efficacy

The safety and efficacy of INTERCEPT-treated PC is supported by the outcome of several clinical trials[12-16] as well as hemovigilance (HV) programs.[17-23]

Randomized Controlled Clinical Trials

INTERCEPT Blood System for Platelets has been evaluated in clinical trials including a total of nearly 1000 subjects that received PR platelets.[12-16] Primary endpoints were met in the controlled, randomized clinical studies that included assessment of corrected count increments (CCI) and bleeding criteria, both of which are measures of hemostatic efficacy. (Table 1)

Table 1: Clinical Trials

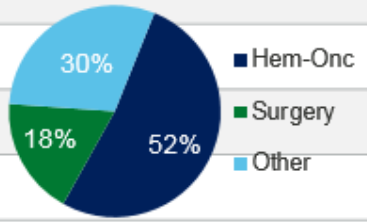
Study Description	Patients	Design	Primary Endpoint	Primary Endpoint Met?
Viability of INTERCEPT Platelets, clearance of amotosalen, healthy patients[12,13]	65	Randomized, single-blind, cross-over	Recovery/survival, clearance of amotosalen	✓
Safety/ efficacy of INTERCEPT Platelets, thrombocytopenic patients[14]	645	Randomized, double-blind, parallel	WHO Grade 2 bleeding	✓
Safety/ efficacy of INTERCEPT Platelets, thrombocytopenic patients[15]	43	Randomized, double-blind, parallel	1 Hour CCI	✓
Safety/ efficacy of INTERCEPT Platelets, thrombocytopenic patients[16]	32	Randomized, double-blind, cross-over	Bleeding time	✓

Hemovigilance (HV) programs provide a comprehensive view of transfusion-related adverse events via the surveillance of blood donations in routine use settings. Over 1.2 million INTERCEPT-treated PC have been monitored through multi-center[17,18] and nationally mandated HV programs,[19-23] with no reported transfusion transmitted bacterial infections (TTBIs), sepsis-related fatalities, or transfusion-associated graft versus host disease (TA-GVHD) reports. A post market surveillance report of a septic transfusion reaction related to PC contamination after INTERCEPT treatment has been reported in the US.[24]

Multi-Center Hemovigilance Programs

Longitudinal studies were conducted at 26 centers across 15 countries.[17,18] Overall, the studied population were primarily patients with hematological malignancies (~50%) and those requiring acute transfusion due to surgery (18%). There were no reported instances of transfusion-transmitted infection TTBI or TA-GVHD; no PC irradiation was performed in over 97% of the INTERCEPT treated PC. (Table 2)

Table 2: Multi-Center Hemovigilance Programs

Study (Years)	INTERCEPT Platelet Doses	Patients	Patient Primary Diagnosis	AEs (SAEs)*
HV1[17] (2003-2005)	5,106	651		0.8% (0.0%)
HV2[17] (2005-2007)	7,437	1,400		0.7% (0.0%)
HV3[17] (2006-2010)	6,632	2,016		0.4% (0.1%)
HV5[18] (2013-2016)	2,373	698		0.5% (0.1%)
Total: (2003-2016)	21,548	4,765		0.6%† (0.0%)

*AE: Adverse Event; SAE: Serious Adverse Event †Conventional platelet AE rate has been shown to be 0.63%

National Hemovigilance Programs

Nationally mandated HV programs in France, Switzerland and Belgium report no TTBIs or fatalities, and no occurrences of TA-GVHD.[19-23] (Table 3)

Table 3: National Hemovigilance Programs

Study	INTERCEPT treated platelet doses	Patients	Outcome	Timing
HV France[19,20]	620,829	~103,000	No TTBIs No TA-GVHD	2006-2018
HV Switzerland[21,22]	282,047	~47,000		2011-2018
HV Belgium[23]	291,879	~48,000		2009-2016
Total	1,194,755	~198,000		2003-2018

Platelet Sustainability/Pandemic Preparedness

Traditional safety measures have significantly improved the safety of the blood supply, largely due to the implementation of routine screening for blood-borne pathogens. However, it's become increasingly evident that a reactive approach such as testing alone may not be a sustainable approach as new pathogens continue to emerge. A host of challenges impede the effectiveness of a reactive approach: test development and regulatory approvals take time to develop, continual addition of incremental tests becomes increasingly costly, and, even in the presence of a test, emerging outbreaks can adversely impact blood availability.[9,10] Unlike reactive measures, PR is a proactive approach in which viruses, bacteria, parasites and white blood cells are inactivated, thus reducing the risk of TTI from contamination of the blood supply.[11]

INTERCEPT PR has helped sustain the local availability of platelets during disease outbreaks. For example, the Zika virus outbreak in Puerto Rico highlighted the difficulties in maintaining an effective donor pool during the crisis. Puerto Rico had the option to suspend collections and import blood components or obtain components locally but perform testing or pathogen reduction. At the time, a testing option was not yet available; Puerto Rico opted for PR to maintain availability of PC.[25] Since that time WHO and the US FDA have issued guidances recommending pathogen reduction as an option to mitigate risks related to ZIKV outbreaks.[26,27]

Other examples in which emerging pathogens have disrupted blood availability include chikungunya and dengue virus outbreaks on Ile de La Réunion, France, in Guadeloupe and Martinique, French Polynesia, and in the Caribbean region; pathogen reduction was implemented in these cases to maintain blood sustainability.[28-30]

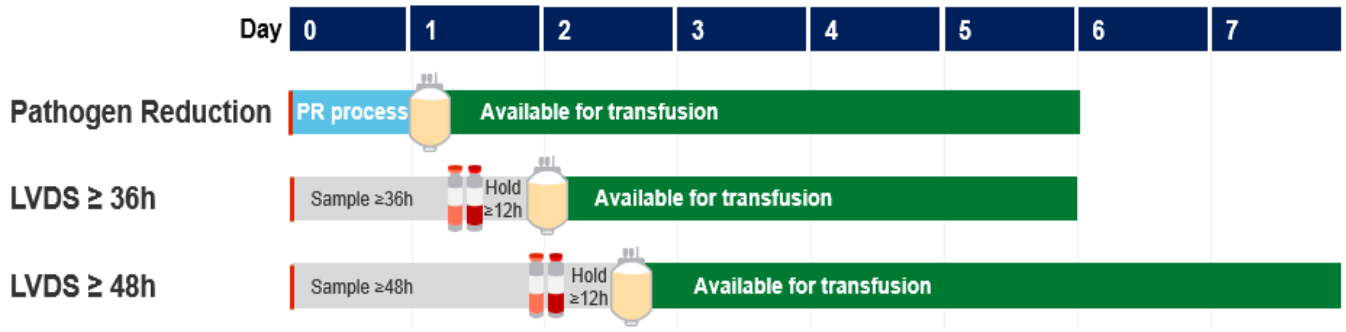
Economic/Operational Value, Optimal Shelf-Life

Operational efficiencies with PR may translate into economic benefits. PR grants hospitals simplicity with a single, ready-to-transfuse solution[1] that complies with FDA malaria,[31] Zika,[27] Babesia[32] and bacterial contamination[1] mandates without the need for testing. Secondary bacterial testing as outlined by some of the FDA Guidance options is not needed,[1] resulting in minimal operational disruption and potential additive cost to hospitals.

Furthermore, PR is the only option that provides the potential to release platelet products sooner after collection; delayed PC release into inventory inherent with culture-based methods is not necessary. Conversely, though culture screening with large volume delayed sampling (LVDS) may offer extended shelf-life, extensive delayed product release is required that prohibits product distribution for the first 48-60 hours. The net effect is a difference of only ~12 hours in effective maximum hospital shelf-life when comparing PR to LVDS. (Figure 1)

Overall, PR offers operational and economic value with the ability to release transfusion-ready product sooner coupled with PR's mechanism of action that inactivates a broad spectrum of bacteria as well as other pathogens, and leukocytes.

Figure 1: Effective Shelf-Life Comparison with Single-Step Strategies



Considerations

Does PR adversely impact platelet count increments (CI) relative to conventional platelets? Should this be a concern as it relates transfusion efficacy?

- Platelet transfusions are intended to stop bleeding; thus, the most direct method to measure clinical efficacy of a platelet transfusion is to assess the prevention and treatment of bleeding (severity of bleeding and number of bleeding events).
- CI is a surrogate marker of platelet survival post-transfusion which does not correlate with bleeding outcomes,[14,33-36] and thus, is a poor measure of bleeding tendency. CI is dependent on a variety of variables, including the patient's underlying condition, platelet dose and processing, and transfusion history.[37]
- A low CI response is commonly caused by the patient's underlying condition (e.g., fever, splenomegaly, drugs, etc.) and may trigger the need for additional investigation to determine cause; however, it does not necessarily indicate a lack of platelet efficacy.
- Some studies have reported a decrease in CI and corrected CI (CCI) with INTERCEPT Platelets when compared to conventional platelets;[14,38] however, multiple studies have shown that hemostasis and platelet and red blood cell utilization are comparable, indicating that INTERCEPT Platelets are effective for bleeding control.[14,34,39-45]

Will use of PR platelets increase the number of transfusions or components use relative to conventional platelets?

- Some publications report a decrease of CCI with INTERCEPT-treated platelets,[14,38] raising the question as to whether this results in increased platelet utilization. Platelet utilization with PR has been studied extensively. Study data vary, with some studies reporting a slight increase in the utilization of PR relative to conventional platelets,[45-47] while large HV studies indicate comparable utilization.[41-44] In all studies, red cell (RBC) component utilization, a measure for hemostatic efficacy, is comparable.[41-47]
- Large-scale HV programs in France, Belgium and Austria[41-44] reported that routine use of INTERCEPT platelets does not lead to increased platelet or RBC component utilization when compared to conventional platelets; this was shown in various patient populations including hematology-oncology patients and patients undergoing surgery. (Table 4)

Table 4: Utilization of Platelet and Red Cell Components in HV Studies

Hemovigilance Studies	Mt. Godinne, Belgium[41]			EFS Alsace, France[43]			Innsbruck, Austria[42]		
	Test (n = 795)	Control (n = 668)	p	Test (n = 2069)	Control (n = 1678)	p	Test (n = 1694)	Control (n = 1797)	p
PC/patient (mean(SD))	10.1(20.9)	9.9(19.5)	0.88	6.4	5.5	<0.05	4.5(8.9)	4.8(9.7)	0.44
Total PC dose/patient	36.7(76.5)	41.5(82.8)	0.24	26.9	24.1	Anova not significant	n/a	n/a	n/a
RBC use/patient	15.0(21.0)	15.1(20.5)	0.9	13.6	13.1	Anova not significant	10.2(13.9)	10.8(15.3)	0.22

  - In a 3-year retrospective analysis, Cazenave et al.[43] reported an increase in the number of PC transfused per patient in the cohort transfused with INTERCEPT platelets when compared to control; however, the total dose of platelets transfused per patient did not differ between study arms. Authors note that platelet content per unit was intentionally reduced as part of routine production during later time periods. Therefore, total platelet dose per patient rather than the number of components transfused reflects true utilization. No significant

differences were found in the total platelet dose per patient, nor in RBC utilization for all patients, including hematology-oncology patients.

- Osselaer et al.[41] reported similar results in Belgium where utilization of platelets and RBCs was analyzed for 3 years before and 3 years after the introduction of INTERCEPT. No significant differences were found in the number of PC transfused per patient, total platelet dose per patient, or in RBC utilization when comparing conventional and INTERCEPT arms; this was found for all patient demographics including hematology-oncology patients.
- Amato et al.[42] and Nussbaumer et al.[44] compared platelet and RBC utilization during two 21-month periods, before and after PR implementation in all populations, including hematology/oncology, surgery, pediatric and neonatal, and trauma subpopulations. Platelet and RBC component utilization were comparable in all populations in both arms. (Table 5)
- Infanti et al.[45] compared platelet and RBC utilization during two 5-year periods, before and after PR implementation in various populations. Red cell and platelet utilization were comparable in both arms for all populations with the exception of the cardiovascular population in which the number of PCs per patient were higher in the test versus control arm. The increased need for PCs in this patient group is due to change in medical practice between test and control, including an increase in number of surgical interventions in patients with antiplatelet drugs for which there were no reversal strategies. (Table 6)
- Retrospective analyses were performed by Yale New Haven in which platelet and RBC utilization were compared between PR and conventional platelets in adult and pediatric patients.[46,47] In adult patients, the number of transfused PC was slightly higher for PR (1.78 transfusions/patient) versus conventional components (1.45 transfusions/patient; $P<0.05$).[47] Conversely, RBC utilization was slightly lower in patients following PR compared to conventional platelet transfusions ($P<0.05$).[47] Similar outcomes were reported for the pediatric population.[46]

Table 5: Utilization of Platelet and Red Cell Components in Austrian HV Study, Patient Subpopulations[42,44]

Cohorts		
Arm (Time Period)	# Patients	# Transfusions
INTERCEPT-Treated Platelets (April 2013-Dec. 2014)	1694	7705
Conventional Platelets (April 2011-Dec. 2012)	1797	8611

Comparable Utilization of Platelet and RBC Components				
Patient Population	# Platelets Transfused		# RBCs transfused	
	Conventional Mean ± SD	INTERCEPT-Treated Mean ± SD	Conventional Mean ± SD	INTERCEPT-Treated Mean ± SD
Total	4.8 ± 9.7	4.5 ± 8.9	10.8 ± 15.3	10.2 ± 13.9
Hem-Onc	9.8 ± 15.7	9.0 ± 15.3	13.7 ± 18.8	13.0 ± 17.0
Cardiac Surgery	2.5 ± 4.0	2.6 ± 3.2	7.3 ± 12.5	7.1 ± 10.7
Pediatric	7.3 ± 16.0	4.1 ± 6.4	7.7 ± 9.7	6.3 ± 5.9
Neonate	2.7 ± 3.1	2.8 ± 3.1	4.1 ± 6.7	5.1 ± 5.8
Massive Transfusion	3.0 ± 2.1	3.3 ± 2.0	16.4 ± 7.4	16.2 ± 7.3

*P value > 0.05 for all, with exception of Pediatric population for # platelets transfused (p= 0.02); decrease in # of pediatric patients undergoing HSCT during test period.

Table 6: Utilization of Platelet and Red Cell Components in Swiss HV Study, Patient Subpopulations[45]

Swiss HV	Heme/Oncology			Allogeneic HSCT			Autologous HSCT			Cardiovascular Surgery			Other Med/Surgery		
	test	control	p	test	control	p	test	control	p	test	control	p	test	control	p
Number of patients	441	355		411	277		130	110		748	414		1079	880	
Number of platelets	4,911	3,806		11,416	6,628		1,173	816		1,817	677		3,262	2,254	
Mean PC/patient (median)	11.1 (4.0)	10.7 (4.0)	0.763	27.8 (18.0)	23.9 (13.0)	0.111	9.0 (4.0)	7.4 (3.5)	0.247	2.4 (2.0)	1.6 (1.0)	<0.001	3.0 (1.0)	2.6 (1.0)	0.119
RBC use/patient (median)	11.2 (6.0)	12.6 (6.0)	0.245	19.3 (13.0)	18.7 (10.0)	0.721	7.0 (2.0)	7.5 (2.0)	0.774	8.5 (4.0)	9.7 (6.0)	0.136	4.1 (0.0)	3.5 (0.0)	0.151

*P value > 0.05 for all, with exception of Cardiovascular population for # platelets transfused (p= 0.001); change in medical practice between test and control, including an increase in number of surgical interventions in patients with antiplatelet drugs for which there were no reversal strategies in test arm.

Are PR platelets associated with higher rates of alloimmunization when compared to conventional platelets?

- The IPTAS trial[48] and subsequent analysis,[49] demonstrated a trend toward *reduced* alloimmunization with INTERCEPT PC. Though not statistically significant, IPTAS reported a 3-fold reduction in high strength HLA class I alloimmunization patients treated with INTERCEPT platelets versus conventional platelets.[48] High strength HLA class I antibodies have been associated with platelet refractoriness while mid to low strength antibodies are not.[50]
- Alloimmunization has been associated with immune refractoriness, or decreased survival of transfused platelets, with the primary concern being a failed platelet transfusion and bleeding.
- Refractoriness (immune and non-immune) is measured via a surrogate marker - platelet corrected count increments (CCI).
- A low CCI response is most commonly caused by the patient's underlying condition (i.e., fever, splenomegaly, drugs, etc.) and does not necessarily indicate alloimmunization.
- The IPTAS trial[48,49] and a prior meta-analysis[51] of all randomized controlled studies did not show any association between INTERCEPT platelets, alloimmunization and refractoriness.
- In a retrospective analysis comparing pre and post INTERCEPT implementation, the Mont-Godinne Blood Transfusion Center in Belgium reported a decrease of clinical refractoriness to platelet transfusion after implementation of INTERCEPT, when analyzing hematology patients requiring repeated transfusions via anti-HLA and anti-HPA screening for alloantibodies.[52]
- The SPRINT trial demonstrated no difference in alloimmunization to HLA, platelet-specific antigens, or amotosalen neoantigens when comparing patients transfused with INTERCEPT treated versus conventional platelets.[14]
- A dog transfusion model demonstrated that INTERCEPT treated platelets led to comparable to potentially improved prevention of alloimmune platelet refractoriness when compared to conventional platelets.[53]

Are PR platelets associated with higher platelet activation when compared to conventional platelets?

- Platelet activation is a series of progressive events triggered by multiple factors which can lead to changes in platelet shape, adhesiveness, aggregation and release reactions. Platelet activation has been associated with refractoriness, or decreased survival of transfused platelets, with the primary concern being a failed platelet transfusion, increase in platelet utilization, and bleeding.
- Many factors may trigger platelet activation, with the state of the donor being the primary contributor. Donor factors include hypertension,[54] type 2 diabetes,[54,55] autoimmune diseases,[57-60]

depression,[61] diet and exercise.[62-65] Other stressors include collection method,[66] excessive agitation, and platelet age.[67]

- Small in vitro studies have suggested that PR may increase platelet activation as assessed by the measurement of microparticles, which are released upon platelet activation.[68] Conversely, a recent study from University of Colorado demonstrated no difference in microparticle content between pathogen reduced versus conventional platelet components; 34.7% of PR and 34.1% of conventional PC revealed activated platelet status based on microparticle content.[69]
- Large HV studies monitoring platelet utilization in routine use, have indicated no increase in platelet or RBC use in all populations with pathogen reduced platelets, including those with hematologic malignancies.[41-44]
- Overall, there is no clear evidence that increased platelet activation and resulting refractoriness or increased number of transfusions occur with pathogen reduced platelets; on the contrary, large-scale clinical and HV studies support the clinical efficacy of pathogen reduced platelets by demonstrating comparable hemostatic properties, as well as utilization of platelets and RBC components.

Conclusion

INTERCEPT-treated platelet components are the platelet product of choice for many US institutions to enhance the safety and sustainability of platelets based on proven product safety and efficacy, the ability to proactively mitigate TTI risk across a broad range of pathogens, and the simplicity it provides hospitals as a ready-to-use solution.

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