ORIGINAL ARTICLE

Development of a quality monitoring program for platelet components: a report of the first four years' experience at Canadian Blood Services

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BACKGROUND: A quality monitoring program (QMP) for platelet concentrates (PCs) was implemented at Canadian Blood Services (CBS) to improve standards and to better understand platelet (PLT) products by supplementing routine quality control (QC).

STUDY DESIGN AND METHODS: Annual surveys of PCs from CBS production sites were conducted, with four completed to date (QMP Cycles 1-4) spanning two different PC production methods: PLT-rich plasma (PRP) and buffy coat (BC). Randomly selected PCs were sent to a central laboratory and tested 1 day after expiry. An expanded panel of tests including CD62P expression by flow cytometry, mean PLT volume, PLT count and morphology, extent of shape change, and PLT metabolic parameters, were applied.

RESULTS: QMP data on the implementation of the BC production method across CBS indicated that BC PCs have less variable in vitro quality measures than PRP PCs. For the QC parameters pH and PLT count per unit, the range of mean values from each site for QMP 3 and 4 fell well within the range defined by regulatory standards, a first step in defining quality benchmarks for PCs. Of the extended panel of quality parameters, CD62P expression was the most sensitive indicator of change and identified an issue with the implementation of the BC PC production method at one site, which was subsequently remedied.

CONCLUSION: A QMP was found to be useful to monitor production processes across sites and highlights best practice approaches while deepening understanding of the quality of PLT products at CBS.

Normal biologic differences among donors mean that a degree of variation is inherent in blood components produced for transfusion.[1] Despite this, blood product providers strive to generate components that are of high quality and are optimally standardized to guarantee safety and effectiveness.[2,3] Quality control (QC) of components prepared from whole blood donations occurs at expiry and focuses on the product's safety and compliance with regulatory standards. For platelet concentrates (PCs), standards include pH, platelet (PLT) count per unit, sterility, and residual white blood cell count if the product is leukoreduced,[4,5] all of which are monitored by routine QC at Canadian Blood Services (CBS). Although production of blood components for transfusion purposes has increasingly adopted a pharmaceutical industry mindset, significant deviations remain in both the use of QC principles and the determination of standards. The panel of standardized assessments currently in use provides general information on product characteristics at expiry, but these standards have remained unmodified for decades and do not encompass

the accumulated understanding of PLT function or the effects of storage on product quality.[6]

Since 2005, CBS has been conducting a quality monitoring program (QMP) for the assessment of its PLT products. The QMP consists of annual surveys of PCs from CBS sites and, while QC tests approximately 1% of product, QMP is conducted on a smaller scale, aiming to test 12 units from each production site per year. A major objective of this program is to improve standards and to better understand the quality of PLTs produced by CBS by applying in vitro tests beyond those used during routine QC testing. Furthermore, samples from all CBS production sites are tested via QMP, permitting examination of the implementation of new processes across the whole organization, as well as site-to-site comparisons to assess the consistency of production practices across a multisite organization. The program was established under the research and development division of CBS as this department has long operated as a centralized troubleshooting facility for product issues and had an established framework for conducting PLT testing. The test panel included several of the more commonly used PLT quality measures because a secondary objective of the QMP was to generate quality benchmarks for buffy coat (BC) PCs using assays beyond the usual QC tests and to explore whether any of these might be useful future routine QC measures.

Here data from the first four annual QMP cycles are presented. PCs were examined at a central research and development laboratory using an extended panel of in vitro quality tests. PLT count per unit and pH, which are also monitored by QC, were measured, as well as PLT morphology, mean PLT volume (MPV), CD62P expression, and measures of PLT metabolism. Between 2005 and 2008, CBS changed its method of component production from whole blood donations, replacing the PLT-rich plasma (PRP) preparation method with the BC method, which results in pooled components consisting of PLTs from four donors;[7] thus we present QMP data from PCs produced using both the PRP method (QMP Cycles 1 and 2) and the BC method (QMP Cycles 3 and 4).

MATERIALS AND METHODS

PLT preparation, shipping and test selection

PCs were prepared by either the PRP or the BC method following CBS standard operating procedures (SOPs) as described elsewhere.[7] All PCs were analyzed a day after expiry (Day 6) in a central testing laboratory in Vancouver, British Columbia, Canada. Components were packed in standard CBS PLT boxes (ISC E-38), with gel packs to control temperature fluctuations and shipped overnight. PCs were shipped either on Storage Day 2 or on Storage Day 4 or 5 and shipping from all sites was less than 24 hours in duration. PCs were stored in a 22°C PLT agitator (either Thermo Forma, Thermo Scientific, Asheville, NC;

or Helmer, Noblesville, IN) under standard CBS storage conditions until testing. Twelve units from each production site were analyzed per QMP cycle. To enable comparison among production years, the selection of tests and procedures was made at the beginning of the study and remained largely unchanged throughout. The test panel for PLT assessment included PLT count, MPV, blood gas and PLT metabolites, PLT activation status, and morphology. Extent of shape change (ESC) was included in QMP 1 and 4.

Sample collection for testing

Before sampling, the blood group, color, and appearance (e.g., redness, lipemic look) of the PC as well as the site from which the component was sent were recorded. Each PC was weighed, and its volume was calculated. PCs were sampled aseptically through a sampling site coupler. Twelve milliliters of PLTs was aspirated into a 20-mL syringe using an 18-gauge needle. From this syringe, 8 mL was used for sterility testing, 3 mL was dispensed into a K_2EDTA vacutainer (BD, Mississauga, Ontario, Canada) for hematology analyzer counts, and the remainder was transferred to a polypropylene tube and used for PLT activation analysis and morphology scoring. A separate 1-mL syringe, which was sealed immediately after sampling with parafilm, was used to obtain samples for PLT metabolic analysis.

Test panel

PLT concentration and MPV

PLT concentration and MPV were obtained from a K_2EDTA tube using a hematology analyzer (Advia 120, Siemens, Mississauga, Ontario, Canada), and PLT count per unit (or PLT yield) was calculated as described previously.[7]

CD62P analysis by flow cytometry

Flow cytometry was conducted on one flow cytometer (Coulter Epics XL-MCL, Beckman Coulter Canada, Inc., Mississauga, Ontario, Canada) for QMP 1 and 2 or another (FACS Canto II, BD) for QMP 2, 3, and 4. During the changeover between instruments, the BD flow cytometer was cross-validated against the Coulter instrument before QMP data collection, with samples analyzed on both instruments and the results used to determine performance and agreement between the two instruments (r = 0.989). Flow cytometric detection of PLT surface antigens was conducted as described previously.[7,8] Briefly, PLTs were diluted with phosphate-buffered saline (PBS) to a concentration of $200 \times 10^9/L$ and stained with a fluorescent antibody cocktail containing anti-CD42-fluorescein isothiocyanate (FITC) and anti-CD62P-phycoerythrin (PE; Immunotech, Marseille, France). Staining was performed

in duplicate for 30 minutes, followed by fixation with 0.2% formol saline (0.2% formaldehyde in 0.9% NaCl) and analysis by flow cytometry. Five-thousand CD42-positive events were collected during each acquisition. Isotype antibodies (IgG2a-FITC and IgG1-PE, Immunotech) were used to control for nonspecific binding. PLTs activated with 1 U/mL bovine thrombin (gift from J. Fenton) served as a positive control.

PLT morphology

Morphology was assessed by modified Kunicki score, as described previously.[7,9,10] Briefly, 50 μL of PLTs was added to an equal volume of 4% paraformaldehyde. Samples, in duplicate, were examined using phase contrast microscopy (100× magnification, Nikon, Mississauga, Ontario, Canada), with 100 PLTs counted per sample, categorized as either discoid (multiplied by 4), spiny (multiplied by 2), or spherical/balloon PLTs (multiplied by 1) and summed to obtain a morphology score. The same two technicians conducted morphology scoring for all QMP cycles. Initially, a comparison of the technicians' scoring was conducted to ensure uniformity of their morphology scores.

PLT metabolic parameters

Measurement of PLT metabolites and dissolved gases was made using a blood gas analyzer (Gem Premier 3000, Instrumentation Laboratory, Orangeburg, NY). The sample was introduced into the instrument according to the manufacturer's procedure within 30 minutes of sampling. Automatically printed results included pH, pO_2, pCO_2, lactate concentration, and glucose concentration.

ESC assay

ESC, which measures PLT responsiveness to activation with the agonist ADP, was monitored using an aggregometer (SPA-2000, Chronolog Corp., Havertown, PA) according to Holme and colleagues[11] and described in detail previously.[7] Briefly, PLT concentration was adjusted to 300×10^9/L using autologous PLT-poor plasma buffered

with HEPES (15 mmol/L final concentration, pH 7.0-7.4). The ESC was calculated by the instrument by integrating optical density readings from PLT-poor plasma and PRP in the absence and presence of ADP (20 μmol/L final concentration). Assays were performed at 37°C.

Statistical analysis

Early in QMP, power calculations were conducted for each parameter to establish sample sizes sufficient to determine significant differences from the population. Based on these calculations and feasibility considerations, a target sample size of 12 PCs per production site per year was chosen. For analysis of data, one-way analysis of variance (ANOVA) and Tukey multiple comparison posttests were performed. Differences were considered to be significantly different at a p value of less than 0.05. Bonferroni confidence intervals for standard deviations (SDs) were calculated and Bartlett's test for equal variance was used to determine whether variances were equal across QMP cycles. Significance of the correlation between different parameters (K > 0.2) was established by using the table of critical values of correlation coefficients.[12]

RESULTS

QMP: averaged results for each annual cycle

QMP 1 was conducted in 2005 and 2006, QMP 2 in 2007 and 2008, QMP 3 in 2009, and QMP 4 in 2010. PRP PCs were analyzed during QMP 1 and 2, and BC PCs were analyzed during QMP 3 and 4. Table 1 displays means and SDs for QMP 1 to 4, calculated across the sites that participated each year. Most parameters that varied across QMP cycles were a direct and anticipated consequence of the change in manufacturing protocols from PRP PCs to BC PCs; for example, the different methods resulted in different PLT concentrations between PRP PCs and BC PCs and the glucose concentration in the anticoagulant for PRP PCs was twice as high as in the BC PC anticoagulant. For

	TABLE 1. Averaged results for QMP 1, 2, 3, and 4*			
	PRP-PCs		BC-PCs	
Parameter (unit)	QMP 1 (n = 106†)	QMP 2 (n = 72)	QMP 3 (n = 96)	QMP 4 (n = 108‡)
PLT concentration (×10⁹/L)	1394 ± 417	1569 ± 463	946 ± 175	947 ± 166
MPV (fL)	8.5 ± 1.0	8.4 ± 0.8	8.3 ± 0.4	8.3 ± 0.4
Morphology (score)	253 ± 24	260 ± 15	284 ± 23	299 ± 20
CD62P (%)	34.8 ± 13.0	47.1 ± 10.3	32.9 ± 6.6	31.7 ± 7.2
pH at 22°C	7.25 ± 0.11	7.15 ± 0.19	7.35 ± 0.09	7.36 ± 0.08
Lactate (mmol/L)	15.6 ± 3.2	16.1 ± 3.7	13.8 ± 1.7	13.4 ± 1.5
Glucose (mmol/L)	28.9 ± 3.1	29.1 ± 3.7	15.0 ± 1.3	14.4 ± 1.2
pO₂ (mmHg)	98 ± 26	98 ± 33	97 ± 20	87 ± 17
pCO₂ (mmHg)	31 ± 9	35 ± 11	38 ± 9	36 ± 6

* Data are reported as means ± SDs for each parameter for each year of QMP, calculated by averaging results from all sites that participated.
† n = 106 for QMP 1 with the following exceptions: pH (n = 92), lactate (n = 88), and glucose (n = 87).
‡ n = 108 for QMP 4 with the following exceptions: lactate (n = 106) and glucose (n = 107).

several parameters not directly related to the change in manufacturing procedure, including morphology, grouping of results between PRP PCs and BC PCs is evident. Tighter SDs were observed for PLT concentration, MPV, CD62P, pH, and the metabolic parameters for QMP 3 and 4 (Table 1), indicating lower variance in the BC PC data for many parameters. To investigate this further, Bartlett's test for equal variances was used to determine whether there were differences in the variances among QMP cycles. For all parameters, there were significant differences in the variances observed across QMP cycles (p = 0.003 or lower), and for many of the parameters, these segregated between PRP PCs and BC PCs, with BC PCs showing lower variances for most parameters. This indicated that the pooled BC product is less variable than the single-donor PRP product.

Standard QC assays: pH and PLT count per unit

To assess the quality of the PCs after shipping using established indices of PLT quality, two QC tests, pH and PLT count per unit (PLT yield), were used. Figure 1 graphs mean results from each site for QMP 3 and 4, against the regulated QC limits, based on AABB standards.[5] AABB guidelines state that pH should be between 6.4 and 7.8 and PLT count per unit should be between 150×10^9 and 450×10^9, with 75% of PCs having a count per unit greater than 240×10^9. For both parameters, but particularly pH, the mean results for each site for QMP 3 and 4 fall within a range much narrower than that defined by the regulatory standards. Despite the narrow range of pH values, ANOVA revealed significant differences in pH among different sites for both QMP 3 (p = 0.02) and QMP 4 (p < 0.01). Whether these differences have any biologic or clinical implications is unknown. Graphing these data reveals a consistency in the results obtained from each site from year to year for pH and PLT count per unit, and the inverse relationship between PLT count per unit and pH is evident (e.g., for QMP 4, the three sites with the highest PLT count/unit, Sites 2, 4, and 7, were those with the lowest pH).

Extended quality testing: results from QMP 3 and 4

Site-by-site analysis of parameters for QMP 3 and 4, arranged by subcategories (PC metabolic measures and PLT characteristics, activation, and responsiveness) are shown in Tables 2 and 3. Significant differences among sites were observed for PLT concentration for QMP 4 (p < 0.01, Table 2), while there were no significant differences among sites for QMP 3. The two greatest mean PLT concentrations observed for QMP 4, at Sites 2 and 7, were significantly different from many of the other production sites. Analysis of PLT metabolic parameters by ANOVA revealed significant differences among sites for QMP 4 for
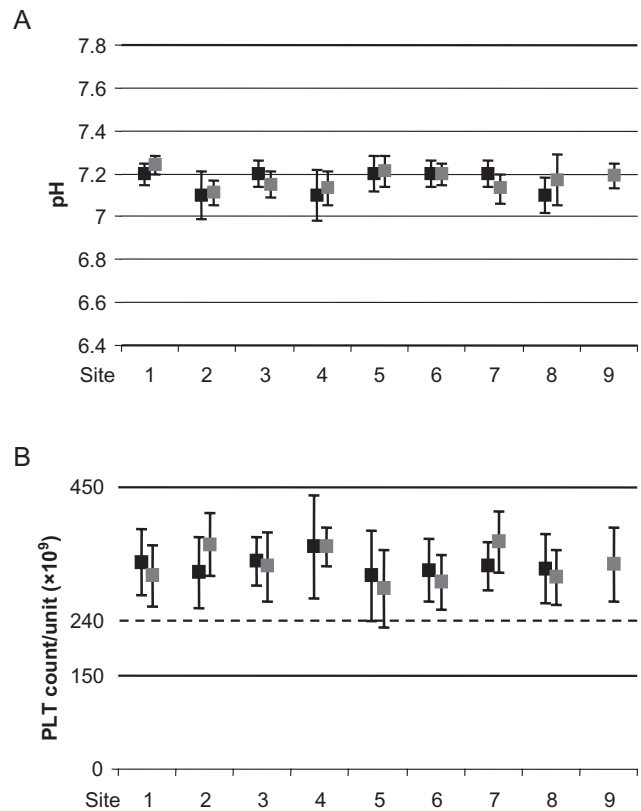
Fig. 1. Site-by-site analysis of pH and PLT count per unit for QMP 3 and 4. Graphs show mean ± 1 SD for pH (A) and PLT count per unit (B) for each participating site for QMP 3 (■) and 4 (■). Regulatory minimum and maximum levels, according to AABB guidelines,[5] are indicated by the bold lines on the graphs: the pH should be between 6.4 and 7.8 in 95% of PCs tested and PLT count per unit should be between 150×10^9 and 450×10^9, with 75% of PCs having a count per unit greater than 240×10^9 (dashed line, Fig. 1B). One-way ANOVA and Tukey multiple comparison posttests were used to determine variance among sites for each year, and significance was accepted at p values of less than 0.05. For pH, significant variance among sites was found for QMP 3 (p = 0.02) and QMP 4 (p < 0.01). For PLT count per unit, ANOVA found significant variance among sites for QMP 4 (p < 0.01) but not for QMP 3 (p = 0.99).

pO_2, pCO_2, glucose, and lactate, although, possibly due to the different power of ANOVA versus the Tukey posttest, the source of the site-to-site differences were determined only for lactate.

No difference among sites was observed for ESC assays, which were conducted in QMP 4 (Table 3). Significant differences in CD62P expression among sites were seen for QMP 3 and QMP 4 (both p < 0.01). The four sites with the lowest CD62P expression were the same for both years of BC production (Sites 1, 2, 4, and 8). Site 6 had the highest CD62P expression for both QMP 3 and 4. In QMP

TABLE 2. Site-by-site analysis of PLT metabolic activity parameters for QMP 3 and 4*

Parameter (unit)	Site									p value
	1	2	3	4	5	6	7	8	9	
PLT concentration† (×10⁹/L)										
QMP 4	880 ± 124	1065 ± 160	931 ± 175	1039 ± 74	850 ± 186	870 ± 105	1083 ± 166	870 ± 126	935 ± 168	<0.01‡
QMP 3	980 ± 159	957 ± 200	950 ± 120	1035 ± 243	883 ± 191	923 ± 150	957 ± 126	929 ± 154	ND	0.59
pO₂ (mmHg)										
QMP 4	84 ± 19	79 ± 12	83 ± 18	80 ± 15	95 ± 20	99 ± 10	81 ± 19	91 ± 14	94 ± 15	0.01‡
QMP 3	87 ± 35	93 ± 15	102 ± 14	95 ± 13	110 ± 26	101 ± 11	102 ± 14	88 ± 12	ND	0.06
pCO₂ (mmHg)										
QMP 4	34 ± 3	38 ± 4	39 ± 7	39 ± 7	34 ± 3	34 ± 3	39 ± 6	40 ± 12	34 ± 4	0.04‡
QMP 3	42 ± 20	37 ± 5	37 ± 5	42 ± 13	33 ± 4	37 ± 4	35 ± 4	38 ± 4	ND	0.23
Glucose (mmol/L)										
QMP 4	14.9 ± 1.2	13.6 ± 1.1	14.3 ± 0.9	14.2 ± 0.9	14.7 ± 1.0	15.0 ± 1.0	14.5 ± 1.9	15.1 ± 0.9	14.2 ± 1.2	0.04‡
QMP 3	14.9 ± 1.0	14.5 ± 1.6	15.4 ± 0.8	14.7 ± 1.3	15.2 ± 0.9	14.8 ± 1.5	15.6 ± 1.1	14.7 ± 1.7	ND	0.35
Lactate§ (mmol/L)										
QMP 4	12.1 ± 1.0	13.8 ± 1.5	13.3 ± 1.2	13.6 ± 0.7	13.1 ± 1.4	14.1 ± 2.5	14.0 ± 1.6	13.5 ± 0.9	12.8 ± 1.0	0.02‡
QMP 3	13.3 ± 1.1	14.3 ± 1.7	13.3 ± 0.9	14.4 ± 2.3	12.8 ± 1.6	13.7 ± 1.7	13.9 ± 2.1	14.9 ± 1.6	ND	0.06

* Data are reported as mean ± SD for each parameter for each site for QMP 3 and 4. One-way ANOVA and Tukey multiple comparison posttests were used to determine variance between sites for each year.
† For QMP 4, PLT concentration at Site 2 was significantly different from PLT concentration at Sites 5, 6, and 8 and PLT concentration at Site 7 was significantly different from PLT concentration at Sites 1, 5, 6, and 8.
‡ Significant at p < 0.05.
§ For QMP 4, lactate concentration at Site 1 was significantly different from that at Sites 6 and 7.
ND = not determined.

TABLE 3. Site-by-site analysis of PLT characteristics, activation, and responsiveness for QMP 3 and 4*

Parameter (unit)	Site									p value
	1	2	3	4	5	6	7	8	9	
MPV (fL)										
QMP 4	8.3 ± 0.4	8.2 ± 0.3	8.5 ± 0.4	8.3 ± 0.4	8.4 ± 0.3	8.3 ± 0.2	8.2 ± 0.3	8.3 ± 0.4	8.3 ± 0.5	0.79
QMP 3	8.6 ± 0.5	8.3 ± 0.5	8.1 ± 0.5	8.3 ± 0.5	8.2 ± 0.3	8.3 ± 0.4	8.5 ± 0.3	8.3 ± 0.5	ND	0.19
Morphology (score)										
QMP 4	304 ± 19	289 ± 18	300 ± 22	304 ± 15	288 ± 30	301 ± 20	298 ± 15	300 ± 17	306 ± 23	0.32
QMP 3	299 ± 12	290 ± 17	277 ± 14	285 ± 21	279 ± 25	272 ± 26	284 ± 22	290 ± 34	ND	0.11
CD62P‡ (%)										
QMP 4	26.6 ± 4.1	27.6 ± 5.8	35.3 ± 5.9	30.2 ± 5.8	31.2 ± 5.8	38.5 ± 10.2	34.6 ± 6.0	28.3 ± 7.8	32.6 ± 3.8	<0.01†
QMP 3	30.8 ± 3.6	30.7 ± 5.7	36.1 ± 6.0	31.4 ± 6.3	34.6 ± 7.7	38.0 ± 6.3	33.6 ± 2.8	28.0 ± 8.0	ND	<0.01†
ESC (%)										
QMP 4	42 ± 11	45 ± 11	37 ± 12	43 ± 8	43 ± 9	40 ± 10	43 ± 9	45 ± 11	38 ± 12	0.44
QMP 3	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

* Data are reported as mean ± SD for each parameter for each site for QMP 3 and 4. One-way ANOVA and Tukey multiple comparison posttests were used to determine variance between sites for each year.
† Significant at p < 0.05.
‡ For QMP 4, CD62P expression at Site 1 was significantly different from CD62P expression at Sites 3 and 6, and CD62P expression at Site 6 was significantly different from CD62P expression at Sites 1, 2, 4, and 8. For QMP 3, CD62P expression at Site 8 was significantly different from CD62P expression at Sites 3 and 6.
ND = not determined.

TABLE 4. Correlation coefficients for PLT quality parameters for the BC PC production method*								
Parameter	PLT concentration	CD62P	Morphology	pH	Lactate	pO_2	pCO_2	Glucose	MPV
CD62P								
QMP 4	−0.01							
QMP 3	−0.1							
Morphology								
QMP 4	0.002	−0.23						
QMP 3	0.15	−0.29*						
pH								
QMP 4	−0.66*	−0.17	0.08					
QMP 3	−0.7*	0.03	0.001					
Lactate								
QMP 4	0.52*	0.16	0.001	−0.5*				
QMP 3	0.56*	−0.16	0.1	−0.6*				
pO_2								
QMP 4	−0.65*	0.2	−0.03	0.6*	−0.3*			
QMP 3	−0.56*	0.05	−0.34*	0.5*	−0.3*			
pCO_2								
QMP 4	0.4*	0.1	−0.008	−0.82*	0.25*	−0.5*		
QMP 3	0.4*	0.01	0.14	−0.5*	0.2	−0.66*		
Glucose								
QMP 4	−0.49*	0.03	0.06	0.5*	−0.29*	0.32*	−0.3*	
QMP 3	−0.59*	0.18	0.3*	0.54*	−0.6*	0.32*	0.2	
MPV								
QMP 4	−0.52*	−0.14	0.15	0.33*	−0.2	0.17	−0.28*	0.26*
QMP 3	−0.34*	−0.1	0.3*	0.26*	0.0	0.03	−0.2	0.1
ESC								
QMP 4	0.17	−0.38*	0.30*	−0.18	0.15	−0.06	−0.09	0.18	−0.17
QMP 3								

* Significant correlation. Consistency of correlation between the parameters was observed for QMP 3 and 4.

3, Site 6 was found to have a significantly higher expression of CD62P than Site 8, and in QMP 4 it was found to be significantly higher than Sites 1, 2, 4, and 8.

Table 4 shows correlation coefficients between pairs of parameters measured for QMP 3 and 4. A striking similarity and consistency of correlation between many parameters was observed for all years of QMP conducted thus far, across both production methods analyzed (QMP 1 and 2 data not shown). PLT concentration correlated significantly with many of the other parameters, particularly those relating to metabolism and, as expected, metabolic parameters tended to correlate significantly with each other. CD62P, which measures PLT activation and secretion, was also found to correlate significantly with ESC, which monitors PLT responsiveness.

PLT CD62P expression among sites

While ANOVA identified variation among sites in many of the extended quality assays, posttests were only able to identify the source of differences for CD62P expression, PLT concentration, and lactate, indicating that these may be the most sensitive indicators of change (Tables 2 and 3). A closer analysis of CD62P expression levels across sites revealed consistent results between QMP 3 and QMP 4 for most sites (Fig. 2) and results for QMP 3 and 4 show a significant correlation with r = 0.89 (p < 0.01).

Site 6 was noted to have the highest CD62P expression during QMP 3 and during the early stages of QMP 4. Also, PCs sent by this site had a noticeably higher amount of air bubbles than PCs sent by other sites, giving them an unusual "foamy" appearance. Despite their unusual appearance, the site producing the PCs was not aware of any issue, and it was only via QMP that this was highlighted. The site was informed and a thorough investigation of the BC PC production method at that site revealed the omission of a step normally done toward the end of production to prevent excess air from entering the components. Introduction of this step resolved the issue of excess air bubbles in the PCs and led to reduced CD62P expression in later samples sent by this site, although overall CD62P levels for QMP 4 for Site 6 remained high with large SDs due to the more activated PCs received earlier during QMP 4.

DISCUSSION

To assess the quality of PCs, standards or benchmarks against which products can be compared need to be established, and these should be sensitive enough to detect even minor alterations in product quality that might occur due to process deviations. Acceptable minimum and maximum values for routine QC measures define ranges into which tested PCs must fall, but within

A

B
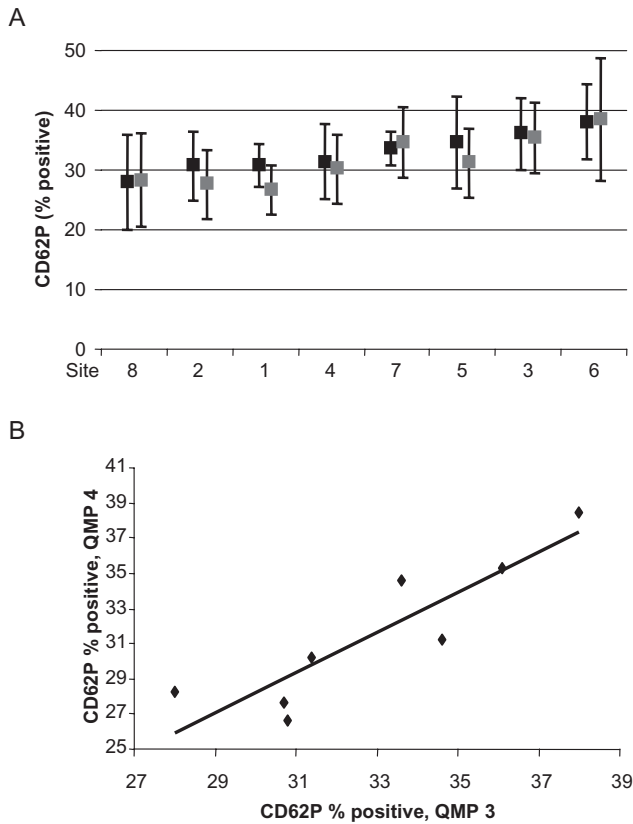
Fig. 2. PLT activation markers for QMP 3 and 4. (A) Mean percentage CD62P expression ± 1 SD for each production site for QMP 3 (■) and 4 (■), ordered from lowest to highest. Site 6 has the highest expression for both years. (B) CD62P expression for each site for QMP 3 versus QMP 4, showing a significant correlation with r = 0.89.

these limits there is much room for variation and a lack of uniformity in the products; thus the ranges are too broad to create benchmarks. Via QMP, the distribution of pH and PLT count per unit within these limits was explored. Both were found to fall into narrower ranges than defined by the regulatory standards. For example, while QC standards define an acceptable pH range between 6.40 and 7.80, the pH of PCs monitored during QMP 4 fell between 6.87 and 7.37. This initial step in describing product specifications for PCs could be used to generate narrower target ranges for production.

Of the extended panel of PLT quality parameters, CD62P and lactate show potential as quality benchmarks for assessing production best practices and the effect of new processes and SOP changes. These are also hallmarks of the PLT storage lesion (PSL), the progressive deterioration in PLT quality, which limits storage to between 3 and 7 days depending on the jurisdiction.[13,14] Although translation of PSL and its hallmarks to a prediction of the in vivo behavior of PLTs posttransfusion remains uncertain,[15] for

the purpose of generating in vitro quality benchmarks, assessing PLT quality in relation to the known hallmarks of PSL is useful.

For example, the increase in CD62P expression associated with PSL is well documented. CD62P expression measures PLT secretion and indicates the level of activation of the PLTs and is extensively used as a PLT quality measure as well as in PLT function tests.[15] Via QMP, significant differences for CD62P expression among sites, ranging between 26.6 and 38.5% for QMP 4, were observed, suggesting the usefulness of CD62P as a sensitive PC quality marker. It is important to note that the clinical relevance of CD62P expression levels or their value as surrogates for prediction of the in vivo behavior of PLTs posttransfusion remains uncertain, despite many studies that have investigated this.[13,16-18] This is in part due to the fact that PLTs are dynamic and can lose surface CD62P and that the relationship between CD62P expression and in vivo viability of PLTs is unclear.[19] Despite its wide use, another issue with CD62P measurement is the huge interlaboratory variability in its measurement.[20] Assessing CD62P during QMP at a single laboratory allowed us to define a normal range of CD62P levels for CBS PCs at expiry.

The timing of the QMP allowed an overview of the implementation of a new production method across the entire organization. A study conducted at a single site during the production method changeover between PRP PCs and the BC production method found that BC PCs have laboratory variables that suggest they are of higher quality than those produced by the PRP method,[7] a finding that agrees with other studies.[21-24] Via QMP, it was noted that, in general, variances among in vitro measures were lower in BC PCs versus PRP PCs, indicating that the pooled BC method produces a more consistent product and that the new method had been successfully implemented across most sites. QMP identified an issue at one site, noted by consistently higher CD62P expression, most likely related to the high amount of air bubbles seen in these PCs.[25,26] Despite the altered appearance of the PCs, this anomaly had not been flagged at the site, but due to QMP the issue was identified and remedied. This highlights two important advantages of a QMP. First, it facilitates direct site-to-site comparisons of products that would not take place otherwise. Second, although all CBS sites operate using the same SOP, differences in practice can occur. Via QMP, sites at which best (or worst) practices prevail can be identified and this information can be used for continuous improvement of both the products and the SOPs.

Shipping and handling of samples can have a dramatic effect on PLT quality parameters.[27] While the shipping procedures from every site were identical, uncontrollable variables were the shipping distance to the testing laboratory and the time without agitation for the PCs. An analysis to determine whether there was a correlation between quality parameters and the distance

between the production site and the QMP research laboratory found no consistent effect. Long periods without agitation can have a detrimental effect on PC quality and metabolic parameters, especially when the PLT concentration is high.[28] All PCs arrived within 24 hours of shipping and were immediately stored with agitation, conditions that should have a minimal effect on PLT quality.[27,29,30] PCs were shipped either early in storage (Day 2) or late in storage (Day 4 or Day 5). An analysis was conducted for CD62P, lactate, and pH to determine whether there were any effects on the quality of the PCs that could be attributed to the day of interruption of agitation. No effects were noted.

For CBS, the real value of the QMP data is that it provides more detailed quality information than QC and allows a better understanding of the product. Specifically, via QMP the implementation of a new process over the whole organization was examined, demonstrating effective implementation as well as the overall higher quality (in terms of PSL markers) of the BC PC product. A production issue that had not been noticed in the manufacturing environment was identified through the QMP process, and the QMP team's expertise was applied to thoroughly investigate and remedy this flaw. While the extended test panel did not reveal much regarding variation in PLT quality among sites, CD62P was found to be a good indicator of change in general. Via QMP, initial steps to look at the range of "normals" for CD62P and the QC measures, pH and PLT count per unit, were taken and this information could be used for future benchmarking. Overall, the additional information generated by QMP proved valuable to our organization and our experiences are a useful guide for other organizations who have implemented or are planning on implementing a similar program.

CONFLICT OF INTEREST

There are no conflicts of interest from the authors of this publication.

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