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# Quality of frozen transfusable plasma prepared from whole blood donations in Canada: An update

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ABSTRACT

*Background:* Transfusable plasma is obtained by processing whole blood donations, by apheresis, or as solvent/detergent plasma (SD plasma), a pooled pathogen-reduced plasma product. The quality of plasma is typically assessed by testing the activities of multiple coagulation-related plasma proteins, due to a lack of clinical trial data linking plasma composition to clinical endpoints. We sought to update previous quality surveys of Canadian frozen plasma (FP; manufactured from single donor whole blood donation and frozen within 24 h of phlebotomy), to provide transfusionists with a more complete picture of its characteristics.

*Study design and methods:* FP units ($n = 131$) were tested for: the activity of factors V, VII, VIII, X, and XI, protein S (PS), $\alpha_2$-antiplasmin (AP), and fibrinogen; and the activated partial thromboplastin (APTT) and prothrombin (PT) times. Comparisons were made to: previous Canadian FP surveys; and to studies of single-donor plasma and SD plasma from other nations.

*Results:* Mean FVIII, fibrinogen, or APTT values did not differ from the previous annual survey of Canadian FP; FV activity was increased and PT values decreased. FP produced with or without leukoreduction differed only in mean APTT. Canadian FP exhibited generally similar quality to that reported by other organizations in Europe and Asia for similarly manufactured single-donor plasma, but contained notably higher PS and AP (~four-fold) activities than did SD plasma.

*Conclusion:* Our results indicate that Canadian FP is of similar quality to single-donor products produced in other jurisdictions. While it is of arguably superior in vitro quality to an SD plasma product recently licensed in Canada, these differences are highly unlikely to have clinical significance for most indications for plasma transfusion.



## 1. Introduction

Plasma is typically transfused to remedy existing or anticipated coagulopathy; in overtly bleeding patients; in those facing invasive procedures and considered to be at high risk of bleeding; or in those requiring plasma exchange to remove abnormal, injurious plasma proteins [1–4]. Plasma made from whole blood donations, in spite of being diluted with anticoagulants, centrifuged, filtered, and frozen during its manufacture, usually contains levels of coagulation factors and inhibitors within the normal ranges seen in freshly drawn plasma from healthy individuals [5]. Regulators in Canada, the United Kingdom, Europe

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and elsewhere focus exclusively on coagulation factor VIII (FVIII) as a marker of frozen plasma quality, likely both for historical reasons and because FVIII is known to be labile [6]. Clearly, many other coagulation proteins influence clotting in both laboratory tests and, judging from the effects of severe congenital deficiencies, in vivo [7]. However, clinical trial evidence is scant, not only with respect to which components of plasma provide the most benefit in its indicated uses [8], but also in terms of the overall therapeutic efficacy of plasma transfusion [9–11]. Investigators interested in plasma quality have therefore resorted to measuring as many coagulation-related proteins in plasma as possible, on the tacit assumption that the best transfusable plasma product will contain as much activity in as many of these proteins as is reasonably achievable [12–14].

Canadian Blood Services (CBS) is a national, not-for-profit blood transfusion service serving the 26 million Canadians who reside outside of the province of Québec. CBS converted from the platelet-rich plasma (PRP) method of processing whole blood donations to the buffy coat (BC) method between 2005 and 2008 [15–17]. This method, widely employed in Europe but not in the United States [18], involves the overnight hold of whole blood at ambient temperature, and automated extraction of plasma away from a platelet-enriched BC formed above a hard-spun red cell layer [16]. In Canada, transfusable plasma made using this method is frozen after more than 8 h and less than 24 h following phlebotomy, and is termed Frozen Plasma (FP, similar to the American product FP24 [19]) as opposed to Fresh Frozen Plasma (FFP). In Canada, FFP is currently made only from apheresis donations, and must be frozen within 8 h of phlebotomy. We previously assessed the quality of Canadian transfusable FP, extending our analysis from the FVIII activity determination required by regulators to include factor V (FV), fibrinogen, and antithrombin activities, and the hemostasis screening tests, the prothrombin time (PT) and activated thromboplastin time (APTT) [17]. We concluded on this basis that the BC conversion had been accomplished without reducing plasma quality [17]. However, this data set suffered from limitations in terms of sample size and number of test parameters.

In this study, we sought to update and improve our characterization of the quality of Canadian transfusable FP. Our specific objectives were: to increase the number of parameters tested to include coagulation factors VII (FVII), factor X (FX), factor XI (FXI), protein S (PS), and $\alpha_2$-antiplasmin (AP); to increase the number of units tested; to expand the data set with respect to donor ABO type and leukoreduction methods; and compare these data retrospectively to previously published surveys. We report: equivalent or higher quality Canadian FP based on coagulation factor activities, compared either to our previous survey values or to those reported in similar studies in the biomedical literature; a lack of influence of leukoreduction techniques on FP quality; and generally higher coagulation factor activities in Canadian FP than in solvent/detergent-plasma (SD plasma), which has very recently become available for transfusion in Canada (August 2012).

## 2. Materials and methods

### 2.1. Blood collection, plasma processing, and sample preparation

FP units were prepared from whole blood donations made at CBS facilities under standard operating conditions, following all applicable Health Canada and FDA regulations, as previously described [17]. Briefly, donations comprised approximately 480 mL of whole blood collected into approximately 70 mL of citrate phosphate dextrose (CPD) anticoagulant, rapidly cooled to ambient temperature on butanediol trays, and maintained at this temperature for up to 20 h [16]. Two collection sets were employed: either "top/bottom" (called "B1" within CBS), if FP, red cells, and platelets were made from the donation; or "top/top" sets (called "B2" within CBS) if only FP and red cells were prepared [17]. B2 units were passed through a whole blood leukoreduction filter prior to separation into FP; B1 units were centrifuged and FP drawn off prior to leukoreduction. All FP units irrespective of which collection set was employed were subjected to the same hard spin of filtered or unfiltered whole blood (accumulated centrifugal force of $7.83 \times 10^7$ to $1.12 \times 10^8$ g min), followed by automated extraction (Compomat G4, Fresenius Kabi, Bad Homburg, Germany) [16] and were frozen within 24 h of phlebotomy. FP units were removed from inventory as an extension of quality control, and shipped to the testing laboratory, situated at McMaster University, Hamilton, Ontario, Canada, from 11 production sites across Canada. Production sites were each requested to provide 12 FP units, as in previous annual surveys [17], 6 made using top/top and 6 made using top/bottom collection sets. It was also requested that half of the units in each sub-group of 6 be type O and the rest non-type O. Eight of eleven sites met these requests, while the other sites provided 12 units each but were prevented from providing the ideal requested mixture by inventory restrictions. While testing was underway, a single type O B2 unit was recalled by CBS for safety reasons; all samples from this unit were destroyed and any data from this unit was excluded from the study. The total number of units was therefore 131 rather than 132. All units were collected in July or August 2009, were shipped to the testing sites on dry ice, arrived at the testing sites in the frozen state, and were stored at −80 °C for at least two months and no more than 12 months (remaining within their 1 year expiry date) prior to testing. FP units were thawed in a water bath (model DH8, Helmer, Noblesville, IN, USA) at 37° for 20 min, aliquoted into four 2 mL aliquots per unit, and re-frozen at −80 °C until tested. Testing for eight of ten parameters reported in this study was conducted at the McMaster University test site, while aliquots were shipped on dry ice to the Centre for Blood Research, Vancouver, British Columbia, Canada, for FX and FXI testing, as described below.

### 2.2. Laboratory testing of coagulation and fibrinolysis proteins

The activity of coagulation factors V, VII, VIII, (FV, FVII, and FVIII), protein S (PS), $\alpha_2$-antiplasmin (AP), and