Quality of Transfusion Products in Blood Banking

Massimo Franchini, MD[1] Enrico Capuzzo, MD[1] Rosalia Turdo, MD[1] Claudia Glingani, PhD[1]

[1] Department of Transfusion Medicine and Hematology, Hospital of Mantova, Mantova, Italy

Address for correspondence Massimo Franchini, MD, Department of Transfusion Medicine and Hematology, Hospital of Mantova, Mantova, Italy (e-mail: massimo.franchini@aopoma.it).

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Abstract

The primary goal in transfusion medicine and cellular therapies is to promote high standards of quality and produce ever safer and more efficacious products. The establishment of a transfusion service quality management system, which includes several organizational structures, responsibilities, policies, processes, procedures, and resources, is now mandatory and widely regulated worldwide. In this review, we summarize the current knowledge on the quality system in transfusion medicine as applied to the production of blood components, including red blood cells, platelets, and fresh frozen plasma.

Keywords

- blood components
- fresh frozen plasma
- red blood cells
- platelet concentrates
- quality controls

One of the leading objectives of blood banks and transfusion services is to promote and maintain high standards of quality, reduce errors, and provide ever more efficacious products. The quality assurance must cover all aspects of transfusion, including donor selection, blood collection, processing, storage, and transfusion.[1–4]

The key role of quality in the transfusion system is well reflected in the standards of the American Association of Blood Banks (AABB)[5] and the Italian Society of Transfusion Medicine and Immunohematology (SIMTI).[6] On the contrary, the adoption of a quality assurance program is mandatory and regulated by the current Good Manufacturing Practice (cGMP) of the Food and Drug Administration (FDA) in the United States[7] and, in Europe, by the Directives 2002/98/EC and 2005/62/EC of the European Parliament, which must be adopted by all member states.[8,9] All these regulatory documents have the scope of harmonizing and transferring the general quality rules ISO:9001, emanated by the International Organization for Standardization (ISO),[10] into the setting of blood banking.[11]

The use of a quality system to support the application of licensing and accreditation standards to the work of a modern transfusion service is particularly critical for the production of blood components because the clinical safety and efficacy of blood transfusion both depend on this process, and specific guidelines on the preparation and quality assurance of blood components have been developed by the Council of Europe.[12]

This review will focus on the quality characteristics of blood products (i.e., red blood cells [RBCs], fresh frozen plasma [FFP], and platelets) in blood banking. The production of plasma-derived products (i.e., clotting factor concentrates, immunoglobulin, albumin) will not be analyzed here, because this is now usually under the control of pharmaceutical industries and not of blood banks.

Red Blood Cells

RBCs are typically obtained by removal of the majority of plasma from whole blood through centrifugation. The great majority of leukocytes ($2.5–3.0 \times 10^9$ cells) and a varying content of platelets are also contained in the RBC fraction, depending on the method of centrifugation. Requirements for a RBC unit include volume of 280 ± 50 mL, hematocrit of 65 to 75%, and minimum hemoglobin content of 45 g per unit. The units of RBC must be kept at controlled temperature between $+2$ and $+6$°C. The storage time depends on type of anticoagulant/preservative solution used (range, 35–42 days).[13] The labeling must comply with national legislation and international directives.[14] In this article, the quality characteristics of the various types (first and second level) of RBC are described.

RBC in additive solution (RBC-AS) represents a blood component prepared by the removal of the plasma from whole blood with successive addition of an appropriate

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additive solution. After centrifugation of whole blood, plasma is removed and the additive solution is immediately added to RBC and carefully remixed. The volume of additive solution ranges between 80 and 100 mL. The vast majority of leukocytes ($\sim 2.5–3.0 \times 10^9$ cells) and a varying number of platelets remain in this blood component, depending on the centrifugation method. Requirements for a RBC-AS unit include hematocrit of 50 to 70% and a minimum hemoglobin content of 45 g per unit.

RBC buffy coat removed (RBC-BCR) is prepared by removal of a major part of the plasma plus the buffy coat layer from whole blood. The leukocyte content should be less than 1.2×10^9 and a varying content of platelets will be present depending on the method of centrifugation. The plasma and 20 to 60 mL of the buffy coat layer are removed from the whole blood after centrifugation, with a resulting loss of 10 to 30 mL of the whole blood RBC. An amount of plasma is retained to provide a hematocrit of 65 to 75%. RBC-BCR can be transfused using bedside filters that further reduce the leukocyte content ($< 1 \times 10^6$). Additional requirements for a unit of RBC-BCR include volume of 250 ± 50 mL, hematocrit of 65 to 75%, and a minimum hemoglobin content of 45 g per unit.

RBC-BCR in additive solution (RBC-BCR-AS) is prepared from whole blood by removal of the major part of the plasma plus the buffy coat layer with subsequent addition of an appropriate additive solution. The leukocyte content should be less than 1.2×10^9 and the platelet content will vary according to the method of centrifugation, but it is usually less than 20×10^9. For preparation, plasma and 20 to 60 mL of the buffy coat layer are removed, resulting in the loss of 10 to 30 mL of whole blood RBC. The additive solution, with a volume ranging between 80 and 100 mL, is immediately added to RBC and carefully remixed. Additional requirements for a unit of RBC-BCR-AS include hematocrit of 50 to 70% and minimum hemoglobin content of 43 g per unit.

RBC leukocyte depleted (RBC-LD) is an erythrocyte component obtained from whole blood donation, RBC, or RBC-BCR after the removal of leukocytes (leukocyte content $< 1 \times 10^6$).[15] Filtration within 48 hours after donation is the technique typically employed to produce RBC-LD. This blood component can be produced by leukocyte filtration of whole blood with subsequent centrifugation and removal of plasma, or by leukocyte filtration of the RBC component. Additional standard requirements include hematocrit of 50 to 70% and minimum hemoglobin content of 40 g.

RBC-LD in additive solution (RBC-LD-AS) is derived from whole blood donation, RBC-AS, and RBC-BCR-AS by removing the leukocytes to a maximum residual content ($< 1 \times 10^6$). Filtration within 48 hours after donation is the technique typically employed to produce RBC-LD-AS, which can be produced by leukocyte filtration of whole blood, with subsequent centrifugation and removal of plasma and immediate addition of the additive solution followed by carefully mixing, or by leukocyte filtration of RBC-AS or RBC-BCR-AS. Additional standard requirements include hematocrit of 50 to 70% and minimum hemoglobin content of 40 g.

Apheresis RBC (RBC-Aph) is obtained by an automated cell separator from a single donor. One or two units of RBC-Aph are collected from the donor's whole blood using a citrate-containing solution as anticoagulant, and plasma is then returned to the donor. This blood component can be used either unmodified or after addition of an additive solution or leukocyte depletion. Requirements of a RBC-Aph unit include hematocrit of 65 to 70% (50–70% when an additive solution is used), minimum hemoglobin content of 40 g, and residual leukocyte content $< 1 \times 10^6$.

RBC can be cryopreserved (RBC-Cryo) with a cryoprotective agent and can hence be stored for prolonged periods. Glycerol is the most commonly used agent and is added to RBC within 6 days of collection.[16] Glycerol is used at either a high or a low concentration to cryopreserve RBC, which are then stored at −60 to −80°C. Both methods require a washing/deglycerolization procedure before transfusion. Requirements of a RBC-Cryo unit include[17] volume > 185 mL, minimum hemoglobin content of 36 g, hematocrit of 65 to 75%, osmolarity < 340 mOsm/L, and residual leukocyte content $< 0.1 \times 10^9$.

Washed RBC is a second-level blood component derived from RBC processing including centrifugation and washing by sequential addition and removal of an additive isotonic solution. Most of the plasma, leukocytes, and platelets are removed. Centrifugation must be performed at a controlled temperature. Hematocrit may vary according to clinical need. Each unit should have minimum hemoglobin content of 40 g and protein content of final supernatant of < 0.5 g. Washed RBC should be transfused within 24 hours from preparation. ►**Table 1** summarizes the main requirements and quality controls of RBC.

Fresh Frozen Plasma

FFP is a blood component for transfusion or for fractionation prepared either from whole blood or from plasma collected by apheresis. FFP must be frozen within a defined period of time and temperature (detailed below) to preserve labile coagulation factors. FFP must contain at least 70 IU of factor VIII per 100 mL and similar quantities of the other coagulation factors and natural occurring inhibitors and, if leukocyte depleted, less than 1×10^6 leukocytes. FFP must not contain irregular antibodies of clinical significance. When used for fractionation, it must comply with the specification of the European Pharmacopoeia.[18]

Methods for FFP preparation listed in the Council of Europe standards[12] include the separation of plasma from whole blood units through centrifugation within 6 to 18 hours after collection if the unit is refrigerated and the separation of plasma from whole blood units held a temperature between 20 and 24°C for up to 24 hours. Rapid freezing of plasma can be accomplished using a system that will allow complete freezing within 1 hour at a temperature below −30°C. For apheresis FFP, the freezing process must start within 6 hours of completion of the procedure using a rapid freezing system as previously described. The labeling of FFP must comply with national legislation and international directives. The Council

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Table 1 Summary of requirements and quality controls for red blood cell concentrates, fresh frozen plasma, and platelet concentrates

Parameter	Red blood cells		Fresh frozen plasma		Platelet concentrates	
	Requirements	Frequency of checks	Requirements	Frequency of checks	Requirements	Frequency of checks
ABO, RhD	Grouping	All units	Grouping	All units	Grouping	All units
HBsAg, HCV-Ab, HIV 1/2-Ab, Treponema-Ab	Negative	All units	Negative	All units	Negative	All units
NAT HCV/HIV/HBV	Negative	All units	Negative	All units	Negative	All units
Volume	Specific for the type of blood component	1% of all units	Stated volume ± 10%	All units	> 40 mL 500–200 mL for PLT-Cryo	1% of all units (minimum 10 units per month)
Hematocrit	Specific for the type of blood component	4 units per month	–	–	–	–
Hemoglobin	Specific for the type of blood component	4 units per month	–	–	–	–
Hemoglobin (supernatant)	Specific for RBC-Cryo	All units	–	–	–	–
Leukocyte content per unit	$< 1.2 \times 10^9$ for RBC-BCR and RBC-BCR-AS $< 1 \times 10^6$ for RBC-LD, RBC-LD-AS, RBC-BCR-LD, RBC-BCR-LD-AS $< 0.1 \times 10^9$ for RBC-Cryo	4 units per month (1% of units for RBC-LD and RBC-LD-AS with a minimum of 10 units per month)	Residual cells: RBC $< 6.0 \times 10^9$/L Leukocytes $< 0.10^9$/L Platelets $< 50 \times 10^9$/L	1% of all units (minimum 4 units per month)	Residual leukocyte content: $< 0.05 \times 10^9$ for PLT-BC $< 0.2 \times 10^9$ for PLT-PRP $< 1 \times 10^6$ for PLT-LD $< 0.3 \times 10^9$ for PLT-Aph $< 0.2 \times 10^6$ for PLT-Cryo	1% of all units (minimum 10 units per month)
Platelet content per unit	$< 20 \times 10^9$ for BCR and BCR-AS	4 units per month	–	–	$> 60 \times 10^9$ for PLT-SU Minimum 2×10^{11} for PLT pool and PLT-Aph > 40% of the pre-freeze platelet content	1% of all units (minimum 10 units per month)
Protein content of final supernatant	< 0.5 g/unit for washed RBC	All units	–	–	–	–
Osmolarity	< 340 mOsm/L for RBC-Cryo	1% of all units (minimum 4 units per month)	–	–	–	–
Hemolysis at the end of the process	< 0.8% of the RBC mass	All units	–	–	–	–
Factor VIII	–	–	≥ 70 IU/100 mL	Every 3 months	–	–
Visual inspection	–	–	No leakage before freezing and after thawing No abnormal colors or visible clots	All units	Presence of swirling phenomenon	All units
pH measured at the end of recommended shelf life	–	–	–	–	> 6.4	1% of all units (minimum 10 units per month)

Abbreviations: Ab, antibody; Aph, apheresis; AS, additive solution; BC, buffy coat; BCR, buffy coat removed; Cryo, cryopreserved; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LD, leukocyte depleted; NAT, nucleic acid testing; PLT, platelets; PRP, platelet-rich plasma; RBC, red blood cells; SU, single unit.

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of Europe allows storage for up to 36 months if the FFP is stored at −25°C or colder, and 3 months if the FFP is stored within the −18 to −25°C temperature range.[12] Storage temperature must be maintained throughout transportation. To preserve labile factors, FFP must be used as soon as possible following thawing, and it must not be refrozen. Before clinical use, FFP must be thawed in a properly controlled environment and the integrity of the pack must be verified to exclude any defects or leakages. No insoluble cryoprecipitate must be visible on completion of the thaw procedure.

Additional comments concern the pathogen-inactivated plasma, which is a blood component for transfusion prepared from a single donation either of whole blood or of plasma collected by apheresis, subsequently subjected to a pathogen-inactivating procedure.[19] It must contain at least 50 to 70% of the labile coagulation factor activities and naturally occurring inhibitors present in fresh plasma. The pathogen-inactivating procedure reduces the risk for enveloped viruses, such as hepatitis C virus, hepatitis B virus, and human immunodeficiency virus. Four methods are used currently, including methylene blue, psoralen (amotosalen), riboflavin, and solvent/detergent treatments.[19] The latter product is manufactured by industries from a pool of plasma (1,000–2,500 donors) that undergoes treatment with the solvent 1% tri-*N*-butyl-phosphate and detergent polyoxyethylene-p-t-octylphenol (Triton X-100). Each unit contains 200 mL of plasma that is stored at −18°C with an expiration date of 12 months. In comparison with untreated FFP, all coagulation factors are reduced by 10%, except for factor VIII and protein S, which are reduced by 20 and 50%, respectively. ►**Table 1** summarizes the main requirements and quality controls of FFP.

Platelet Concentrates

The quality controls in platelet concentrates depend on the method used for their production. One of the most important parameters is the platelet count, because this is related to the clinical efficacy of this blood component.[20] Another important issue that must be accomplished before storage and transfusion is the demonstration of the swirling phenomenon, based on light scattering by platelets of normal morphology in movement.[21] There is actually no requirement to evaluate the activity of stored platelets through functional tests. The platelet concentrates can be produced from whole blood or directly from a single donor through an apheretic procedure. Two main methods are used to prepare platelets from whole blood. The first is the platelet-rich plasma (PRP) method, consisting of a low-speed centrifugation followed by a high-speed centrifugation and the removal of the resulting supernatant platelet-poor plasma (PPP), leaving a final PRP volume of 50 to 70 mL. Finally, the platelets are allowed to disaggregate (using a sodium citrate anticoagulant) and are then resuspended. The second method includes the preparation from buffy coat and consists of a hard spin of whole blood that enables the removal of the supernatant PPP from the top of the container and the RBC from the bottom of the container into separate transfer packs. The remaining buffy coat is further processed to obtain a platelet concentrate. A platelet concentrate prepared from a single PRP or buffy coat unit must contain more than 60×10^9 platelets. Four to six PRP or buffy coat units derived from whole blood donations are usually pooled to produce a platelet concentrate with a therapeutically effective dose of platelets suspended in plasma.[22]

Apheresis platelets are a blood component obtained by a single donor, using automated cell separation equipment. The utility of this method consists of reduction in the risk of anti-HLA alloimmunization. Furthermore, apheresis platelets may be useful for the transfusion of already alloimmunized patients. The reduction in the number of donors also reduces the theoretical risk of transmission of blood-borne viruses. Regarding the quality parameters, platelet content should be minimum 2×10^{11} per unit with a maximum residual leukocyte content of 0.3×10^9 cells.

Platelet concentrates obtained from PRP, pooled buffy coats, and apheresis may also be leukocyte depleted through filtration or other in-process steps. Prestorage leukocyte depletion is recommended (within 6 hours after preparation if performed by filtration).[23–25] The three products may be stored in an additive solution to minimize the risk of transfusion reactions associated with plasma proteins and prevent the risk of transfusion-related acute lung injury.[26]

Cryopreserved platelets are prepared by the freezing of platelet concentrates at −80°C within 24 hours of collection using a cryoprotectant (dimethyl sulfoxide 6% weight/volume or glycerol 5% weight/volume).[27] The platelets are thawed, washed, and resuspended in autologous plasma or an isotonic additive solution before use.[28] ►**Table 1** summarizes the main requirements and quality controls of platelet concentrates.[29]

Conclusions

From the analysis of the current knowledge, it appears clear that quality assurance management plays a key role in blood banking, as it regulates all transfusion activities. If the application of newer technology tools for the assessment of the quality of transfused blood components is warranted, then the national health systems should also encourage and support improvements in transfusion service quality.[30–32] The common aim of such actions will be to provide ever safer and more clinically effective blood products.

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