Guidelines for the Blood Transfusion Services

8.5: Evaluation of plasma for fractionation for the manufacture of immunoglobulin

http://www.transfusionguidelines.org/red-book/chapter-8-evaluation-of-novel-blood-components-production-processes-and-blood-packs-generic-protocols/8-5-evaluation-of-plasma-for-fractionation-for-the-manufacture-of-immunoglobulin

8.5: Evaluation of plasma for fractionation for the manufacture of immunoglobulin

8.5.1: Introduction

In establishing any novel component, the development process is expected to involve three stages (see Table 8.1d):

- I**nvestigation (Phase 0):** Initial intensive investigation of a range of parameters on a relatively small number of units (e.g. 10 -16) to establish concepts. This should involve *in vitro* studies with serial sampling. Components produced during this phase should not be used for fractionation. For clarity, the guidance on which tests need to be performed is shown in Table 8.5.

- **Validation (Phase 1/Phase 2):** Operational validation on a larger number of units (e.g. 125) to establish routine operation of the technique, using a small set of parameters selected on the basis of the above studies to allow setting of routine quality parameters. It may not be necessary to test all subset parameters on the full number of units and a risk-based approach should be used if the number of tests for a given parameter is going to be reduced.

- **Routine (Local process validation):** Ongoing routine validation using parameters selected on the basis of the above studies. Advice may be sought from SACBC on the validation requirements for plasma for the manufacture of immunoglobulin produced from automated processing of whole blood or other technologies that are not specified in Table 8.5.

  The blood services' fractionation partner may have additional requirements.

8.5.2: In vitro evaluation of novel frozen plasma for fractionation

8.5.2.1: Suggested study design

Because of the wide normal range of some plasma proteins and potential inter-batch variation of assays, it is suggested that novel units and controls be produced and assayed in parallel, with the novel technology being the only variable. A less costly alternative, if logistics permit, is to do a pooled paired comparison, where two units are pooled, and one half processed by the novel technique. This provides greater statistical power for fewer units assayed, and is particularly important for storage studies. As it may not be appropriate to compare plasmapheresis and whole blood derived plasma, data could be compared against manufacturer's claims or published literature where there isn't a comparable plasmapheresis process in place.

The number of units to be studied should be based on the study objectives and design and determined by statistical analysis based on the difference between test and control units to be detected. A sample size of at least 16 test or controls is suggested for the evaluation of new fresh frozen plasma/cryoprecipitate components for transfusion and this same sample size is suggested here if using an unpaired study. Fewer

units (>=10) will be required if a pooled and split study design is used, however this approach will not be suitable for all studies, e.g. for studies looking at contact activation where individual donor susceptibility is important. While ABO group may not be as relevant here as when levels of FVIII and von Willebrand factor are considerations, it is recommended that validation should include an equal mix of group O and non-group O donations.

Ideally provision should be made for storing and testing paired units or aliquots from each unit at every time point, as thawing out three or four different packs at each time point introduces excessive variation. However, a pre-validation should be done to ensure that the behaviour of the aliquoted component during storage is the same as that in full sized units.

8.5.2.2: Assays required

The extent of any evaluation depends in part on the degree of novelty of the method used to collect plasma. Table 8.5 gives a summary of which assays are recommended in different situations. Advice may be sought from SACBC on the validation requirements for plasma components for fractionation produced from automated processing of whole blood or for the manufacture of other blood products not specified in Table 8.5. Sections "8.4 Evaluation of new fresh frozen plasma/cryoprecipitate components for transfusion" and "8.6 Generic protocol for the evaluation of apheresis equipment" should also be consulted if the collection device is new and/or intended for multiple purposes e.g. plasma for fractionation and clinical plasma (FFP). Where appropriate, methods must be those recommended by the European pharmacopeia or a validated equivalent method, for example total protein.

Before freezing:

- volume, platelet count, WBC*, RBC

*Particularly relevant to plasma which has been collected by any filtration technique. If filtration is done outside the collection procedure, assays should be performed before and after filtration.

During storage:

- Samples should ideally be tested after one to four weeks of frozen storage at <=-20°C freezing to assess the quality of frozen plasma. Tests should be those presented in Table 8.5 and include:
    - total protein, Albumin, IgG
    - markers of unwanted activation of coagulation e.g. prothrombin fragment 1.2, fibrinopeptide A, factor XIIa, thrombin-antithrombin (TAT) complexes. It is important to measure markers of activation for the manufacture of immunoglobulins as there have been reports of batches of immunoglobulins ‘contaminated’ with FXIa, resulting in thrombotic events
    - optional tests – prothrombin time (PT), activated partial thromboplastin time (APTT) and FVII, FVIII and Fibrinogen. These tests are not relevant for the manufacture of immunoglobulins but should be considered to future proof against the use of plasma for the manufacture of labile proteins such as clotting factors. A complete validation would be required before fractionation to produce clotting factor concentrates could commence.

Table 8.5 Evaluation of novel plasma for the manufacture of immunoglobulin

Table 8.5 gives a summary of which assays are recommended for the manufacture of immunoglobulins only. Advice may be sought from SACBC on the validation requirements for plasma for the manufacture of labile proteins such as clotting factors.

Assessment [1,2]	Whole blood derived	Apheresis derived	Novel filter
Volume[3]	✓	✓	✓
Leucocyte content[3]	✓	✓	✓
Platelets[3]	✓	✓	✓
Red cells[3]	✓	✓	✓
Plasma Haemoglobin[4]	?	?	?
Total protein	✓	✓	✓
Albumin	✓	✓	✓
IgG	✓	✓	✓
Markers of unwanted activation of coagulation[5]e.g. TAT, Frag1.2, FPA, FXIIa, FVIIa, FXIa, C1 inhibitor, S2302	✓	✓	✓
PT ratio, APTT ratio[6]	?	?	?
FVII, FVIII, Fibrinogen[6]	?	?	?
Complement C3a, C5a[4]	?	?	?

[1]Where appropriate, methods must be those recommended by the European pharmacopeia or a validated equivalent method

[2]Additional assays may need to be performed to comply with requirements from fractionators

[3]Tests are only required prior to freezing

[4]Parameter may be required by fractionators – needs to be confirmed. If required parameter will become mandatory

[5]Included due to reports of batches of immunoglobulins ‘contaminated’ with FXIa, resulting in thrombotic events

[6]Recommended to future proof against the use of plasma for the manufacture of labile proteins such as clotting factors