SUPPLY PROJECT

"Strengthening voluntary non-remunerated plasma collection capacity in Europe"

REPORT ON THE RESULTS OF THE:

"Characterization of the waste of recovered plasma and missed opportunities for plasmapheresis in European Union"

D3.4

This report is part of the project "101056988/SUPPLY" which has received funding from the European Union's EU4Health Programme (2021-2027).
The content of this report represents the views of the author only and is his/her sole responsibility; it can not be considered to reflect the views of the European Commission and/or the European Health and Digital Executive Agency (HaDEA) or any other body of the European Union.
The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains

Table of content

Introduction

This D3.4 report is the result of work done in collaboration between

Dr Luis Larrea, Centro de Transfusión de la Comunidad Valenciana, Spain
Dr Sys Hasslund, Aarhus University Hospital, Denmark
Dr Mafalda Ribeirinho, Instituto Português do Sangue e da Transplantação, Lisboa, Portugal
Dr Sébastien Merrien, LFB, France
Dr Matthias Johnsen, DRK-Blutspendedienst Nord-Ost, Institut für Transfusionsmedizin Dresden, Germany
Dr Françoise Rossi, International Plasma and Fractionation Association – IPFA, The Netherlands

The waste of plasma in Europe is mainly due to the inability to process all plasma recovered from whole blood donations and, to date, to a lost opportunity to collect plasmapheresis plasma for fractionation. This situation has created an EU dependency on PDMPs prepared from US plasma Given the criticality of PDMPs, the consequences of this waste on the supply of PDMPs to patients are significant, most notably in times of crisis. To address this shortfall in EU plasma supply in the future, activities within this task focus on developing appropriate recommendations for countries and/or blood establishments on how to maximise the recovery of plasma or implement plasmapheresis collection for plasma for fractionation (PfF), to establish a reasonable level of Strategic Independence in the European Union (EU) (i.e., cope with a lack of delivery of PDMPs in times of crisis).

To establish this objective, a three-phase strategy has been followed, including a survey of 15MSs on quality parameters allowing us to provide recommendations.
This report describes the so-called “transfer plan”, aiming at supporting swiftness in BEs collecting PfF and in the long run, implementing a harmonised Quality Management System in these BEs.

Aim of the transfer plan

Our task within WP3 has established an overview of 15/16 MS BEs management of collecting Plasma for fractionation with regards to wastage and miss opportunities for plasmapheresis collection. Several levels were identified to reduce the waste, improve the plasmapheresis collection already in place, or initiate a plasmapheresis program. This has been described in Deliverable D3.3.

The intermediate recommendations based on our survey and documented in Deliverable D3.3 serve as a basis for providing a Transfer plan. This is performed with a few pilot BEs, volunteers among candidate BEs, by providing a comparison of existing practices in the MS with each of the D3.3 recommendations. It also identifies main gaps in existing quality management systems versus regulatory requirements for each country/Blood Establishment.
Through this comparison analysis, we found that the model in each of the candidate BEs revealed to be different, allowing the establishment of a focused transfer plan for each situation.
Further suggestions are also described.

The Transfer plan encompasses

- Ways for implementing Plasmapheresis collection, or improvements,
- Quality management references,
- Toolbox of templates to be used for sending PfF to fractionators.

Choice of the Selected and responding BEs

BEs from the 15 survey respondents collecting plasma for fractionation, were active collecting recovered plasma and active or not in collecting plasmapheresis plasma.

Among them, five were targeted as candidates. Our choice was based on the possibility of implementing plasmapheresis collection or improving an already practice.
Invitation to participate in this step was sent to the 5 BE organisations and 3 answered positively, Portugal, Spain and Denmark.

Description of the current situation in the country

The three countries selected for this task show different current situations. They all wish to raise collection of plasma for fractionation locally.

- Country A is a medium size EU Member State already active in the frame of collection of plasma for fractionation. Both recovered and source plasma are collected in similar volumes. Plasma is sold to fractionators. Collection by apheresis is already implemented in one plasma centre already active.
- Country B is a medium size EU Member State already active in the frame of collection of plasma for fractionation. Currently, only recovered plasma is collected, and volumes are quite small. Implementation of collection of source plasma may be an option, but at this stage no firm plan has been endorsed.
- Country C is a major size EU Member State already active in the frame of collection of plasma for fractionation, involving in contract manufacturing. Plasma is sent to fractionators and the PDMPs are returned to the country for delivery in the hospitals. Recovered plasma is mainly collected in this country so far. 10 % of total volumes are already collected by apheresis. Initiatives to raise collection volumes of source plasma have recently been started.

Process of the exchanges with the 3 contributing BEs

Key contacts in blood establishments have been identified for this task. They all work either at national or regional level and have been active in the field, with excellent knowledge of the specificities of plasma for fractionation. Most of them were already aware of the EU-SUPPLY initiative. After a first exchange, they were proposed to read our D 3.3 report in which first recommendations are highlighted. As first feedback, they were happy to allow time to think of the situation of PfF as working in a blood banks, although this does not represent their core activities, and these activities are not prioritised. For our team, this is a key point which reinforce the actual need to share with EU Blood Establishments ready-to-use solutions in the perspective to enhance collection of PfF in order to save time. In all cases, sufficient resources should be allocated, in particular in defining a dedicated position as program or project lead with matrixing project team.
As a second step, we proposed to exchange more practically on operational aspects of the collection of plasma for fractionation. A specific form was used in which main recommendations from report D3.3 had been selected and it has been used to start the analysis against current practices with the objective to identify if improvements may be identified and would be feasible.

The next chapter describes these operational aspects.

Comparison with D3.3 recommendations

Recommendation on switching from bags to bottles

The type of container may influence the available volume of PfF. Most plasma collected in the private sector is packaged in solid plastic bottles. In EU blood banks, where mainly recovered plasma is collected, usually only packaging in bags is considered.
In the case source plasma is collected and dedicated to further manufacturing, our recommendation is to prioritise the use of bottles. The benefits are multiple: this is associated to cost reductions, improvement in freezing and storage operations, and, when regarded at the level of the whole process until thawing of plasma at fractionation level, the use of bottle instead of bags for source PfF may result to limit the loss of plasma volumes of 2 to 4 %, mainly linked to the fact that less broken units enter the fractionation plant and at time of thawing of plasma, less residual plasma is wasted when the plasma is packaged in bottles.
Some EU BEs (i.e. in Germany) already switched from bags to bottles for plasma for fractionation, after agreement with fractionators. We are convinced this should be a key driver for the future in EU Blood Establishment which will collect more and more source plasma in the coming future. This is confirmed by the exchanges we had with the three blood establishments:

- Country A: Might be an option
- Country B: Agrees with the proposal but concerned by the technical complexity of the switch
- Country C: None are using bottles, everyone is willing to, asking how to move forward.

A clear consensus has been observed on the interest to consider this switch for source plasma when further oriented to plasma for fractionation. However, technical barriers seem to limit this switch. Based on the experience of some German Blood Establishments, a dedicated document has been prepared by our group in order to explain the pros and cons of such change and provide technical recommendations. This document can be found in Appendix 1.

Another additional benefit could be the lesser proportion of microbial contaminations of bottles as compared to bags. This is going to be explored when working further on this transfer plan.

Recommendations for reducing the plasma volume of platelet concentrates

Platelet apheresis source of additional PfF

Moving from 100% plasma platelet to 30% plasma platelet in some MSs would also be source of additional PfF.

Platelet concentrates typically have a volume of 200 to 350 ml. In the past, platelets were suspended in 100% plasma, either from one donor or from all donors (pooled platelets).

Plasma in platelet concentrates has beneficial as well as disadvantageous effects in the recipient[i, ii, iii, iv.] However, several platelet additive solutions (PAS) were developed to overcome the deleterious effects of plasma.

A dedicated document has been prepared by our group to explain the pros and cons of such a proposal and provide technical recommendations. This document can be found in Appendix 2 of the report.

Here again, the 3 MS/BEs have different practices and experiences.

- Country A already collects apheresis platelets in 35% donor plasma and 65% PAS, however, has no experience in collecting additional plasma during the apheresis procedure. A multi component donation in this setting is considered interesting. Country A will have to look further into the technical and safety details of this procedure.

- Country B only collects platelet by apheresis using 30% plasma plus additive solution
- Country C uses PAS since 2001.

Two out of the 3 BEs have actually implemented this plasma saving procedure and the third one is open to looking into this proposal. This data is supporting this recommendation to all BEs.

Plasma from First-Time Tested Donors (FTD)

We suggest that donations from First time plasma donors should be considered more acceptable for fractionation.

If the regulatory framework allows for fractionation plasma from FTDs, obviously when appropriately justified, in particular in assessing the residual risk to miss positive donations (i.e. during the window periods of testing kits), the use of this plasma for fractionation would contribute to more volumes. This is all the more justified, when such units are accepted for transfusion (which for the safety measures are different from what is applied on PDMPs, as the manufacturing process undergoes dedicated biological safety steps).

- Country A takes currently only samples from new donors.
- Country B does not perform plasmapheresis, however, would agree with this approach.
- Country C does not differentiate FTDs and regular ones, i.e., uses the full donation from FTDs.

This recommendation, to be applied to European BEs, would need to set up a working group in order to align rationales. Then, recommendations could be provided to the European institutions.

Selection of donors/testing criteria

- Dedicated Plasmapheresis donor questionnaire

The final destination of source plasma for fractionation and plasma for transfusion is totally different and thanks to the processing steps of plasma derived medical products, the same requirements are not applicable in comparison to labile products. However, in most EU BEs, the same requirements apply.
The EU blood directive as well as the Blood Guide clearly distinguish the requirements of both types of plasma, in particular for the criteria on selection of donors and testing requirements.
However, in practice, the same selection and testing strategies are applied at the level of most EU Blood establishments whatever the destination of plasma is used, because in certain settings, the destination is not known at first.

This proposal has been discussed with the three countries.

- Country A is currently using the same questionnaire for blood and plasma donors but handle information (i.e. travels and medication) depending on the type of donation.
- Country B who although does not perform plasma apheresis for fractionation, agrees with this suggestion
- Country C is studying this possibility and has not taken any decision until now.

Two countries confirmed they do not ask different questions which may orient some donations not authorized for labile products to plasma for fractionation only, and one asks different questions.

Moreover, two of the 3 countries do not have plasmapheresis-only-centres. Country A has a facility where they only collect plasma for fractionation, however the department and organisation do both. And the donors can be allowed to donate plasma for fractionation as well as full-blood donation at a different location.

There is a double advantage of defining a dedicated questionnaire for plasmapheresis plasma for fractionation: first, a specific questionnaire would allow dedicated BSs to save resources; second, when a donor is identified as excluded for transfusion, it would be readily available for plasmapheresis and here again, this pathway would save resources and retain donors.

When switching from paper to electronic questionnaires, designing two dedicated questionnaires depending on donation type would facilitate the use of the proper questionnaire for plasmapheresis. An electronic questionnaire integrated in the donor path for donation would be more quality reliable, diminishing the chance of error leading to discard of the product.

Examples of donor questionnaires with dedicated questions can be found in the Toolbox, section Templates_Dedicated Donors Questionnaire for plasmapheresis plasma for fractionation.

Specific donor selection criteria for apheresis PfF should be implemented at national level in all EU MSs.

If the EU regulations foresee some specific requirements depending on the final destination, the EU blood banks may be limited by their national regulations. Amongst the three Blood establishments interviewed, this has been especially highlighted by Country C. We recommend that in the frame of the SoHO Regulation implementation, all NCA lift their additional national requirements for PfF and are strictly aligned to the EU requirements (unless obviously justified by a specific local epidemiological situation).

In practice, with regards to biological safety:

- Donors having travelled in countries at higher risk for Chagas and Malaria should not be deferred when the plasma is oriented to plasma for further manufacturing only.
- Testing donations for Malaria, Chagas, Syphilis is not mandatory when the plasma is oriented to plasma for fractionation only.

When this is not already the case, our group recommends adapting the quality system to enable donors and donations to be oriented to plasma for fractionation, when possible, even if not authorized for plasma for transfusion.

- We also discussed the possibility of adapting the testing methodology strategy.

In particular, NAT testing in EU blood banks is usually performed on individual donations and very small minipools. This requirement is aligned to the safety risk for labile products. In the case of plasma for fractionation, the size of minipools may be increased, depending on the performance of the testing kits and the requirements of the overall safety strategy of the fractionators. Usually, fractionators require testing in minipools $\leq$ 96 donations. In the case blood banks are able to define the orientation of the plasma depending on their final destinations, different testing strategies may be implemented. This is associated with major cost reductions, and particularly relevant when source plasma collection dedicated to plasma for fractionation is active in a Blood Establishment. This is applicable in some EU Member States (i.e. Germany, The Netherlands or France). The three Blood Establishments contributing to this transfer plan will assess this option, as they all use individual testing.

With regards to biological parameters,

- Country A does not apply different testing.
- Country B agrees with this suggestion.
- Country C uses the criteria of WB donors except for the periodicity and Ig and protein levels. The removal of certain unnecessary markers is under review by the CA.

Such testing differentiations, both for biological safety and biological markers between blood product for transfusion donations and plasma for fractionation apheresis donations, would lead to lower rates of deferral, therefore contributing to the increased donor base. This would well apply not only for dedicated plasma-only centres, but also for combined WB and apheresis donation centres. These changes can be considered as key drivers, leading to cost reductions also, when an estimate of ~15€ could be saved per litre of PfF.

Changes in the regulatory environment

Medical staff

- Donor examination could be performed by a trained nurse

The three Countries agree with this proposal.

- Country A has implemented examinations and medical interviews to be done by trained secretaries and a few nurses; Blood pressure and pulse, or judgment of veins to be done by trained nurses.
- Country B agrees 100% with this suggestion, given the lack of medical staff
- In Country C sometimes is done by a trained nurse

- Collection of plasma can be performed by a trained phlebotomist

- Country A has trained nurses or trained medical students for phlebotomy
- Country B agrees 100% with this suggestion, given the lack of medical staff
- In Country C it must be done by a trained nurse

- Physician to be reached by teleassistance as necessary

- In Country A, this his is current practice
- Country B agrees 100% with this suggestion, given the lack of medical staff
- In Country C, the physician should always be present.

Because of the practice and views of the 3 countries contributing (as well as other EU MSs), we recommend that the current rules requesting the physical presence of a responsible physician within the BEs for donor-related supervision and activities in BEs be changed for more flexibility, allowing trained nurses, medical students or even secretaries for donor examination and trained nurses or medical students for collection of plasma. The responsibility of a physician shall remain, allowing this function to be performed through teleassistance when needed.

Such changes would be key in BEs efficiency.

Education and donor management

Systematic communication and education of donors is highly needed in all BEs; Implementing actions and regular national campaigns for plasmapheresis donations to increase the rate of donation per inhabitant.

- In Country A, efforts are currently made with regards to Education of personnel, to answer donors' questions and presenting posters, and video for social media related to diseases treated by PDMPs. To some degree, the donor drive is taken care of partly by a national donor organisation able to coordinate "campaigns". Also, some money is brought back from the organisation to sponsor a full-time employee for marketing background, for larger

campaigns and reach out to larger companies for a drive. This country is suggesting also to communicate on donor health and donation frequency. They consider communication as a good motivation for donations for PfF.

- Country B finds this very relevant when implementing the plasma apheresis program. it also fully agrees and highlights that donor organizations and associations should also contribute to the use of communications tools.
- Country C is trying to establish a marketing campaign including education.

These answers confirm the element highlighted in our first report, that is the need to increase the donor base and frequency of donations in several MS, even in those collecting a large volume of PfF but who are not efficient enough in relation to the donor contribution of the population (some MSs have only below 4% of the population who donates and a frequency of 2-3 per year).

Development of collection in mobile units

Collection of plasma can be as convenient and close to donors as possible, if donors are not compensated in the same way as in the private sector but donating through a civic gesture.

- In Country A, there is no such plan. In fixed sites, there is 1 nurse attending 4-5 donor seats. The question of efficiency is raised, such as how many donors could fit in a mobile unit. Also, there is no mobile collection of whole blood, due to local conditions making it hard to put it in practice, including challenges with electricity (need for back-up generators). This country is using rather smaller facilities, like hospitals labs.
- Country B agrees with the initiative. In the future, when implementing a plasma apheresis program, this criterion will be considered. Additionally, it considers collection done in stores, shopping centres or big urban areas.
- Country C has just begun collection in mobile units through a program in two regions in 2023 and will continue in another one in 2024.

This last country is highly active in finding pathways to increase the collection of PfF, including in collaboration of plasmapheresis machines manufacturers. Their experience could be shared in the future with other countries in a more detailed transfer plan. From this, we would like to highlight the opportunity to improve the communication through the European Blood Alliance network. Contact with the organisation of EBA working groups (Benchmarking WG and/or the Innovation and new Products WG) will be made.

MSs which do not yet collect plasma by apheresis and government pragmatic support for upgrading collection of PfF

- *Funding (Will of the MS authorities)*

- In Country B, there are close to 30 hospitals BEs collecting blood components. The national authority has not yet achieved that all these BEs perform full plasma utilisation. However, this is a priority goal, and a zero-waste programme has been defined. For this, a plasma apheresis programme will be launched when the technical and logistic aspects as well as resources and an adequate number of donors will be set in place towards a full fractionation programme.
- Country C also benefits from the MS authority support and shows a dynamic towards efficient plasma for fractionation collection: the ministry of health has been financially supporting the BEs to spend in plasma collection (marketing campaigns, mobile apps, plasma kits). This year the amount would round up to 2 million €.

This shows that MS authorities play a key role in the development of the collection of PfF in the public sector.

Size of the country and potential volumes available for fractionators

- *Harmonisation of plasma collection in the EU public sector*

None of the countries had strong vision on the possibility of working with other countries with low volumes. As some of them are currently working on harmonisation at the Regional/ National level, which would build for an only later step.

- *Harmonized templates of Quality agreement with fractionators*

- Country B states this would avoid wasting time fulfilling questionnaires
- The two other Countries agree

This harmonisation is realised within this transfer plan.

- *Mixing of plasma origins would be facilitated*

Currently, there is no mixing of PfF between different MS in the EU.

- Neither Country A nor Country B, working on a regional framework, allow the mixing of plasma of these different regional origins within their respective country,
- Country C is in the process of switching from regional tenders to national tenders, allowing mixing of regionally collected plasma within this MS.

Working on harmonisation at the Regional/ National level, which would build a first step towards mixing plasma of different MS origins.

One of the other 16 EU MSs is working with such a regional model, however monitoring the supply of the derived-PDMPs through the whole MS. One could suggest that an economy of scale would be reached by going forward to a national tender model, that is actually used by another MS, also organised in regions for the collection of plasma.
We believe that switching from regional tender to national tender would help the harmonisation of quality management practices, as proposed in Country C. This could be applied to other MS, working at regional levels. And it would also be a step forward to the further in time possibility of mixing plasma from different MSs, if collecting too small volumes, to be accepted by a fractionator.

System of accreditation unified at EU level for public sector

- Country C benefits from a dedicated entity that depends on two scientific societies, and grants accreditation to BEs and transfusion services at hospitals following guidelines based on GMP and European guidelines. This is not mandatory, while in each region, there is an accreditation system from the local authorities that is mandatory, that makes inspection from the legislative point of view.
  Eighty-two % of BEs of this country have been accredited[v].
- The two other countries do not have such a system, only CA inspections

Our proposal for the future is studying the possibility to implement an accreditation system for all the European BEs, that would allow to harmonise the practices and have a lean process utilised by all.
See below chapter “Plan for harmonisation of PfF collection within the European public actors towards an accreditation system.”

Recommendations adaptative to the country situation

As seen through out this report, the three BE/MS that cooperated to this transfer plan have different status with regards to PfF and plasmapheresis collection, different MS's support, and can be organised either around regions or nationally.
With recommendations that cover all settings, each MS could benefit from the very improvements corresponding to their situation. Some of them highlighted in the transfer plan, would be adapted for a certain setting while others for another. Some recommendations are more universal (as bottles or platelet plasma) and can be adopted by any MS/BE.

Also, based on this transfer plan, more advanced MS/BE can be taken as ambassadors for the ones who are making efforts to increase the volumes of PfF collection and improve the efficiency of the processes. A strong interconnection between BES is highly needed.

Plan for harmonisation of PfF collection within the European public actors towards an accreditation system.

Our aim beyond the SUPPLY project, is to provide an 'accreditation' or 'recognition" or else 'validation' system for BEs in the European MSs, whether in the EU/EEA or larger Europe, who collect plasma for fractionation in the public sector.
With such a tool, BEs collecting PfF would benefit from a standard to apply in quality management of the collection of PfF; in audits from either fractionators, or a membership association; and enable them to receive an acknowledgment of their high level of quality for the collection of PfF. When many BEs, in several MS, would have been 'accredited', we can consider that the quality of the plasma they collect is at a similar level.
This would: 1) Increase the attractivity of their plasma for fractionators, as a lower level of investment would be needed on their part; 2) Facilitate the acceptance of their plasma by fractionators; 3) allow in the long term the mixing of plasma from different sources (MSs).
The final outcome being the increase of plasma collected in Europe that would be manufactured into PDMPs.

In positively working on this possibility of evaluating how to build this 'accreditation' system, we are studying national accreditation programmes, the AABB accreditation system for transfusion blood components, as well as the EGALiTE project, dedicated in Europe to SoHOs as Blood-Tissues and Cells, to take advantage of a working method.

Our aim is to evaluate how much we could work in collaboration with these systems, for the principles that would be the foundation of ours, dedicated to the specific SoHOs that is plasma for fractionation.

Reference to AABB accreditation

AABB's standards and accreditation programme are proposed internationally as quality management system approach, standards as essentials with technical requirements designed to ensure optimal quality and safety for donors, patients and staff of such accredited facilities, with regards to blood components for transfusion. It encompasses collecting, processing, testing, distributing, and administrating blood and blood components.

AABB's accreditation has phases depending on the first site, additional site or a new activity feature of the centre, and processes with a self-assessment step, then an on-site audit step. When accredited, a site goes through the accreditation process every two years.
These AABB standards and accreditation allow minimal variability within the centre and among international facilities. Because AABB's cover the transfusion part of a BE's activities, there is an obvious need for a similar type of standards and accreditation for the collection, processing, testing, storage and distribution of plasma for fractionation, whether collected by apheresis or recovered from whole blood donations in BEs.

Reference to EGALiTE

The EGALiTE – EU4HEALTH (egalite-europe.eu) ***E**uropean **G**roup dedicated to the possible **A**ccreditation and **L**iaison of Blood-**T**issues and Cells **E**stablishments.*
Blood products are addressed here in their transfusion destination.
WP5 is responsible for defining EGALiTE Accreditation Programme for SoHO entities, which includes:

- *The "Accreditation Dossier," where all future accreditation procedures, including audit guidance, methodologies, and harmonized templates, are defined based on EU good practices. Documents included in this dossier are the Accreditation Guide, Applicant's Guide, Application Form, Audit procedures, and Auditor Job Description.*
- *The "EGALiTE Standards" intended to apply to all actions performed by SoHO entities in the preparation of SoHO, covering donor recruitment, selection, evaluation, testing, and SoHO collection/procurement, sampling, quality control, processing, preservation, storage, release, and distribution for clinical application. The structure of the standards includes a chapter dedicated to Quality Management and transversal principles associated with handling SoHO, as well as specific chapters dedicated to donation, collection, processing, storage, and distribution of SoHO. Different specific chapters are included for various tissues and cell activities.*
- *A digital "Accreditation Platform" that will simplify procedures related to the submission of applications for accreditation, self-assessment of applicants, audit and evaluation, reporting, and issuing of certificates.*

The programme is still under development, as the project is ongoing until October 2024. It defines, among other tools, a Core Standard for all SoHOs dedicated to being used for clinical purposes, directly administrated to patients.

Our project

- As described above, within the SUPPLY project, we wanted to build the foundations for assuring that harmonisation of practices and standards is needed; and if so, to assess how much MS's BEs are motivated to participate in this exercise; and to commit to continue this plan of actions after the SUPPLY project is over. At IPFA, we have the strong wish to propose using a platform to develop this 'accreditation system', with the participation of BEs. Most likely, on-site work would be ultimately needed for implementation, and this could be done with the contribution of both IPFA and volunteer BEs.

  For the future, IPFA could take the lead to evaluate the possibility of a foreseen collaboration with the EGALiTE group, with regards to the three tools, "dossier," "standard" and "plateform", applied to PfF.
  Ultimately, such tools could also be used for blood establishments outside of Europe.

Next steps

- In order to comfort our approach and the quality items to reinforce, we would continue exploring the comparison of other MS BEs' current practices with D3.3 recommendations, to receive and study a wider range of expectations.
- With selected and volunteer BEs, we would develop the pathway to creating the pragmatic 'accreditation' system. Contact with EGALiTE coordinators has been made and this is currently discussed between the SUPPLY and the EGALiTE projects, as a starting block.
  Our coordination with the EGALiTE programme would relate to Plasma for fractionation.
  In a further project, possibly led by IPFA, *dedicated Standards for PfF* would need to be developed and possibly owned by IPFA, in close collaboration with EGALiTE members, that is BEs members of EBA collecting PfF, EBA itself, and with coordinators of the EGALiTE project.
  The use of the EGALiTE platform when built and the development of its "satellite PfF" counterpart is also an option that has been formulated with the project coordinators. This would also require the participation of volunteer BEs.

- If the SUPPLY project finds a follow-up, this could also be part of a second leg.

Conclusions

This work, following the previous collection of data from 15 MS, has allowed the objectivation of practical improvements that are needed to optimise and make more efficient the collection of PfF. With the 3 BE/MS contributing to this transfer plan, we were able to identify specific areas where to bring emphasis of improvement and harmonisation. Great enthusiasm was shown by these BE officers.

As already described by the WP4, our work confirmed and in further details, the disparity of the organisations and methods used in the various BEs of Europe. It highlights the need for national Health institutions to engage in a strategic program for the collection of PfF, which should include financial support.

On the other hand, in each MS, areas of waste, even if modest, have been identified. Leaner pathways and methods can gain in efficiency, spare financial resources, and optimise the volumes of this precious SoHO starting material of medicinal products. The more the quality management system is harmonised, the more plasma can be proposed to fractionators, at a BE level, regional level, and national level. And the more, small volumes collected by MS countries with more modest population could be pooled and fractionated into PDMPs, increasing the availability of these, manufactured from European plasma, hence releasing more and more the European dependency of third countries like it is the case currently with the US.

Documentation for a transfer plan

Toolbox

Quality management Standards

- EDQM_guide-to-the-preparation-use-and-quality-assurance-of-blood-components-21st-edition.PDF
- COMMISSION DIRECTIVE 2016-1214 quality system standards & specifications for BEs_CELEX_32016L1214_EN_TXT (GPGs)
- Eur. Commission_Eudralex_GMP_Vol4_annex14_rev30-03_2011_en
- Eur.Pharmacopeia_10.6 plasma for fractionation 0853E_eff012022
- PE 005-4 PICS Good Practice Guidelines for Blood Establishments and Hospital Blood Banks
- WHO - National Standards Blood Transfusion Services_2013-01
- WHO Guidance on centralisation of Blood donation testing and processing.9789240020825-eng
- WHO Guidance on Increasing supplies of plasma-derived medicinal products in low- and middle-income countries_9789240021815-eng
- WHO_GMP for Blood Establishments - Annex 4 - N961-2011-07
- WHO-ECBS-2005-annex-4-human-plasma-fractionation
- 21 CFR Part 606 (up to date as of 11-01-2023)
- AfSBT_Step_Wise_Accreditation_Standards_2014
- Directive 2002/98/EC on quality and safety standards for the collection, testing, processing, storage and distribution of human blood and blood components

  Additional implementing acts:
  - Commission Directive 2004/33/EC on the technical requirements for blood and blood donation
  - Commission Directive 2005/61/EC on the traceability requirements and notification responsibilities in case of serious adverse reactions and events
  - Commission Directive 2005/62/EC that sets out Community standards and specifications relating to the quality system for a blood bank
- Please refer also to the SoHO Regulation as will be soon published

Templates

- Checklist of assessment of compliance to requirements (self-assessment)
- Checklist of audit of compliance to Good Practices/Specifications
- Template for viral markers assessment according to EU PMF requirements
- Template for change control procedures
- Template of quality agreement – recovered plasma
- Template of quality agreement – source plasma

Acronyms

AABB: Home - Association for the Advancement of Blood & Biotherapies (aabb.org)

EBA: European Blood Alliance

EDQM: European Directory for Quality of Medicines

EGALiTE: European Group dedicated to the possible Accreditation and Liaison of Blood-Tissues and Cells Establishments EGALiTE – EU4HEALTH (egalite-europe.eu)

EU: European union

BE: Blood establishment

FTD: First-Time tested Donors

GDP: Gross Domestic Product

GMPs: Good Manufacture Practices

IPFA: International Plasma and Fractionation Association

IQPP programs: International Quality Plasma Program

IRL: Ireland

MRB: Marketing research bureau

MS: Member State

PAS: Platelet additive solutions

PfF: Plasma for fractionation

PfT: Plasma for transfusion

PDMP: Plasma-derived Medicinal Product

QA: Quality Assurance

SoHO: Substances of Human Origin

US: United States

vCJD: Variant of the Creutzfeldt-Jakob Disease

WB: Whole blood

WHO: World Health Organization

Appendixes

Appendix 1 / Rationale for collecting source plasma in bottles

Pro bottles

Reducing loss of plasma after donation

In the course of the collection of plasma, the air in the disposable apheresis kit transfers to the final container. Collection of the plasma in bags results in the accumulation of a reasonable volume of air in the bag. Freezing bags partially filled with air is disadvantageous because bubbles of air remain at the inner surface of the bag. Bubbles of air between the deep-frozen plastic and the plasma cause a high risk of breakage in course of the further handling.

After the donation, operators must squeeze the plasma bag to transfer the air into the disposable. During this strenuous process, variable amounts of plasma end up in the disposable, reducing the volume of plasma available for fractionation.

One plasma centre evaluated this loss: the difference between expected and measured volume for ~3000 donations collected in bags vs. bottles was 7 ± 5 ml (all donations within 20 ml of expected volume were evaluated, 130 excluded due to this restriction; larger differences due to donation/donor issues). A large number of small additional plasma yields sums up to almost 100 litres per year.

Plasma bottles are equipped with a sterile air filter that allows air to leave the system. After donation, this filter must be sealed. The elimination of manual plasma extraction more than compensates for this additional production step. It is only a second tube weld in addition to the one required for both bags and bottles. The operators have been very pleased with the change from bags to bottles, especially because it has eliminated the tedious de-aeration step.

Plasma freezing

Usually, plasma in bags is frozen in a contact shock freezer or an ultra-cool air ventilation freezer. Loading and unloading these machines is quite time-consuming.
Plasma bottles can easily be frozen in standard stackable plastic racks (e.g. for water bottles) directly in the deep-freezing storage room or a compartment/tunnel of the room with additional cooling capacity.

Container breakage

Frozen plasma bags are quite fragile, especially at the welds. Even with de-aeration, very careful handling during packing, transport and unpacking of the units, up to 1 % have to be discarded due to breakage. Plasma bottles are much less susceptible to breakage, as they do not have protruding thin plastic parts.

Residual Plasma in container

The loss of plasma in the container at the fractionator depends on the type and size of the container. The loss is 1-3% lower for bottles than for plasma in (large) bags. For bags, the relative loss also depends on the bag size, being less favourable for small volumes in large bags. There is no such dependence for plasma in bottles, the loss is close to zero. Because of the constant ratio plasma/anticoagulant, fractionators might accept even very low volumes of apheresis plasma in a bottle. Small volumes, due to donor or machine problems, are not very common, but donors will be pleased to know that even this small donation is making a difference.

Contra bottles

Packing

The main disadvantage of bottles is the unfavourable ratio of the number of containers in a carton to the size of the carton. A carton of 12 bottles could easily hold 100+ bags for on-site connectable source-plasma kits. Limited storage space at the donation centre or central storage can be offset to some extent by improved logistics.

The difference on deep-freezing storage space required for plasma bottles versus plasma bags is less unfavourable. One pallet can hold 640 plasma bags versus 540 plasma bottles.

Appendix 2 Recommendations for reducing the plasma volume of platelet concentrates: Platelet apheresis source of additional PfF

All commercially available PAS require a certain amount of residual plasma, typically 30%, in the platelet concentrate to achieve an optimal product.

The amount of plasma carried over to the platelet concentrate can be easily adjusted:

For apheresis machines, kits for multi component donations allow the donation of 1 to 2 platelet concentrates in 30% plasma, along with 400 to 500 ml of extra plasma suitable for transfusion or fractionation.

Buffy coat pooled platelets can be produced with higher haematocrit buffy coats, providing 30 % plasma for final volume.

A volume of 140 ml to 245 ml of plasma per pooled platelet concentrate can be gained by switching from 100 % plasma to 30 % plasma/70 % PAS.

The cost of the PAS and an additional sterile welding (latter only for buffy coat method) is lower than the benefit of additional plasma.

---

[i] Gulliksson H, Platelet storage media, Vox Sanguinis (2014) 107, 205–212

[ii] de Wit YES et al. Platelet concentrates in platelet additive solutions generate less complement activation products during storage than platelets stored in plasma. Blood Transfus. 2023 Mar;21(2):157-167

[iii] Mertes PM et al., Hypersensitivity transfusion reactions to platelet concentrate: a retrospective analysis of the French hemovigilance network. Transfusion, 2020. 60(3): p. 507–512.

[iv] van Hout FMA et al,. Transfusion reactions after transfusion of platelets stored in PAS-B, PAS-C, or plasma: a nationwide comparison. Transfusion. 2018 Apr;58(4):1021-1027. doi: 10.1111/trf.14509. Epub 2018 Feb 6. PMID: 29405304.

[v] "https://www.catransfusion.es/" The CAT Foundation is a certification organization in the field of transfusion medicine, cellular and tissue therapy, established by the Spanish Society of Hematology and Hemotherapy and the Spanish Society of Blood Transfusion and Cellular Therapy, which has a Board of Trustees, a Secretariat and a Technical Committee.