International Society of Blood Transfusion (ISBT) Working Party (WP) on Global Blood Safety (GBS)

Recommendations on increasing availability of recovered plasma for fractionation

Recommendations in this document are made by the ISBT WP on GBS in the context of improving quality and safety of recovered plasma to meet industry and regulatory requirements for fractionation to prepare essential plasma-derived medicinal products (PDMPs). Additionally, achieving quality and safety of recovered plasma suitable for fractionation is inherently linked with advancing the quality, safety and availability of blood components for transfusion.

Need for reducing wastage of recovered plasma

PDMPs including several clotting factors and normal immunoglobulin are recognized on the WHO Model List of Essential Medicines. However, their supply is insufficient to meet patient needs, especially in the developing world. At the same time, it was estimated in 2015 that more than 9 million liters of plasma that could be recovered annually from donated whole blood ("recovered plasma") is not produced, or is discarded. In low and medium income economies, recovered plasma generated in excess of the therapeutic needs for transfusion is generally destroyed because it does not meet the quality and safety criteria applied by regulators in developed countries to plasma for fractionation.

This wasted plasma, if produced following current international quality and safety requirements, could meet the criteria for industrial fractionation thereby allowing the manufacture of a range of PDMPs such as albumin, coagulation factors (factor VIII, prothrombin complex, factor IX, fibrinogen, etc.), and polyvalent immunoglobulin, that are currently under shortage in the emerging world.

Availability of such plasma fit for fractionation would represent an important source of life-saving PDMPs, meeting therapeutic needs of patients suffering from various hematological pathologies and other conditions. If no action is taken, the volume of plasma wasted but potentially useful to make PDMPs, will continue to rise as a result of (a) increased blood collections in emerging countries to meet the justified needs for red cells, and (b) persisting weaknesses and gaps in Good Manufacturing Practices (GMP).

Reasons for the wastage of recovered plasma

There are multiple reasons why recovered plasma is discarded instead of being made available for fractionation. They encompass both organizational and technical limitations that prevent recovered plasma from reaching the quality and safety standards needed to manufacture PDMPs at the industrial scale.

Generally speaking, appropriate collection, testing, processing, storage and distribution practices as well as quality systems are missing in developing countries and make recovered plasma not meeting the requirements for fractionation in facilities that are following industrial international regulations and standards. Reasons typically include: lack of a national policy and legal framework for blood collection; absence of national regulatory authority for blood collection and processing including inspections of blood establishments; scarcity, diversity, and lack of standardization in blood collection, testing, processing and storage practices; and lack of financial and human resources to upgrade blood establishments to a level needed to produce plasma qualifying for fractionation. Blood establishments in developing countries often lack equipment for controlled centrifugation, for rapid freezing or adequate cold-storage of plasma, and for sensitive and efficient testing for infectious diseases (e.g. NAT for HIV-1, HCV and HBV). In addition, basic quality management functions are often very weak or absent, above all documentation and traceability, quality assurance, and mechanisms for corrective/preventive actions.

When basic requirements in production of recovered plasma for fractionation are not met, established plasma fractionators are not able to accept plasma for fractionation under contract ("contract fractionation") or acquire plasma in exchange of plasma products, and any intent to establish a domestic fractionation plant in a resource-limited country comes with substantial risks (financial, organizational and others.)

Recommendations

General Recommendations:

1. A situation assessment and gap analysis should be undertaken to provide a clear and comprehensive understanding of the needs, challenges and opportunities in the country regarding the need for safe plasma-derived medicinal products;

2. The results and conclusions of these critical analyses should orientate the country in identifying best options for its population and making judicious choices for policies and strategies to address risk and unmet needs (e.g. choice of treatment schemes and therapeutic products);

3. Such an assessment and analysis should be conducted at the national level against the internationally recognized quality and safety standards;

4. National capacity for local production of recovered plasma suitable for fractionation and for local preparation of safe blood products should be encouraged and strengthened based on the situation assessment and gap analysis;

5. Existing blood establishments in developing countries should improve their operations and processes, reaching such levels that blood products can be prepared safely and continually, including use of pathogen reduction technologies whenever achievable.

6. A realistic action plan should be elaborated following and based on such an assessment and analysis and put in place with full support from government, to address identified weaknesses and deficiencies and to implement appropriate corrective actions at the level of blood regulation and blood component preparation;

7. Adequate human and financial support for appropriate plasma production and local safe blood products should be provided by governments, both to the regulatory authority and blood collection establishments.

Specific Recommendations

1. Recovered plasma obtained in all countries should be considered as source material for fractionation if it can be produced under conditions meeting internationally recognized quality and safety standards;

2. The program to improve the quality and safety of recovered plasma for fractionation should aim concurrently at upgrading the quality and safety of blood components for transfusion such as red blood cells, platelets, fresh frozen plasma and cryoprecipitate;

3. National Regulatory Authorities in developing countries need to be strengthened to assume their responsibilities in the context of plasma for fractionation (i.e., setting standards and guidelines, conducting inspections, giving necessary approvals, granting marketing authorizations for fractionated products resulting from local plasma, etc.);

4. Implemented actions should be consistent with international recommendations and science-based guidelines on safe blood collection, testing, processing, storage and distribution practices applicable to plasma for fractionation for example as elaborated by the World Health Organization;

5. Production of recovered plasma for fractionation should be coordinated at the national level, but can be initiated progressively starting from major blood establishments in the country and gradually expanding to smaller blood establishments;

6. Production targets for the volume of recovered plasma for fractionation should be tailored to the country situation and be appropriate to meet the national clinical needs for albumin, coagulation factors and immunoglobulin.

7. Implementation of a national plan to produce recovered plasma for fractionation should be based on realistic perspectives in acquiring needed know-how and initiating a contract plasma fractionation program; or, under carefully studied conditions, domestic fractionation.

Summary and Conclusion

Although there is a global shortage of plasma products, available recovered plasma that could be used for fractionation is currently discarded as it does not meet minimum quality requirements. The production of plasma for fractionation and especially fractionation itself come with significant costs and needs for expertise that currently may be difficult to master and implement in many developing countries. Nevertheless, wasting of recovered plasma is unacceptable in consideration of the unmet need for essential PDMPs that could be made from this plasma. PDMPs made from recovered plasma that is discarded could help to alleviate existing product shortages, including Essential Medicines, in developing countries. Wasting of recovered plasma also may be considered unethical as it disregards the full societal value of altruistically donated whole blood. In addition, implementation of blood separation to support component therapy when justified can generate more plasma that could be used for fractionation. For such medical and ethical reasons, efforts should be made in developing countries to elevate the standards for blood collection, testing, processing into components, storage and distribution to enable production of quality and safe recovered plasma acceptable for fractionation. The recommendations provided in this document are intended to enable developing countries to identify and take the steps necessary to improve production standards in blood establishments, thereby facilitating patient access to safe blood components for transfusion and increasing patient access to essential PDMPs.

Reference documents:

WHO Recommendations for the production, control, and regulation of human plasma for fractionation. https://www.who.int/bloodproducts/05-2019%20Human%20plasma%20fraction.pdf

WHO guidelines on good manufacturing practices for blood establishments. https://www.who.int/bloodproducts/publications/GMP_Bloodestablishments.pdf

Improving access to safe blood products through local production and technology transfer in blood establishments. https://www.who.int/phi/publications/blood-prods_technology_transfer.pdf

WHO Model List of Essential Medicines, 20th List (March 2017) http://www.who.int/medicines/publications/essentialmedicines/en/