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Self-sufficiency challenges of blood products in LMICs and role of diplomacy

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Abstract

Purpose: PDMPs are one of the therapeutic substances derived from human blood and have a role in treating several life-threatening diseases. PDMPs are also included in the WHO Essential Medicines list. PDMP production development has been successful in developed countries. In contrast to LMIC countries, blood management is far from the standard. This issue is undoubtedly a challenge for developing countries. Besides, health diplomacy is suitable for solving the gaps in some health system problems. **Methods:** This writing uses a systematic review to collect information related to the challenges experienced by developing countries in implementing plasma fractionation and strategies that are ably implemented to increase the supply of PDMP. **Results:** The main challenges in implementing domestic fractionation by LMICs are collecting raw materials that need to meet standards, finances to fulfill fractionation facilities, and the need for more local teams with expertise in plasma fractionation. This also highlights how health diplomacy utilization can fill the gaps. **Conclusion:** Technological transformation is the key to success at each stage of the implementation of contract fractionation towards domestic fractionation, which will strengthen the resilience of the pharmaceutical industry in each LMIC country. It is also necessary to consider the benefit of establishing health diplomacy.

Keywords: self-sufficiency; cooperation; blood products; LMICs; health diplomacy

INTRODUCTION

Plasma Derived Medicinal Products (PDMPs) are one of the therapeutic substances from human blood. In human blood, whole blood components and others are important in health services. WHO reported that only 56 of 171 reporting countries produce plasma-derived medicinal products (PDMP) through the fractionation of plasma collected in the reporting country. Additionally, 91 countries reported that all PDMPs were imported, and 16 reported that no PDMPs were used during the reporting period [1].

PDMPs are prepared by the pharmaceutical industry that manages human blood plasma through plasma fractionation and produces plasma-derived drug products such as albumin, coagulation factors, and immunoglobulins which are life-saving therapies for several chronic and acute life-threatening diseases [2]. Currently, plasma-derived products have no substitutes, which causes these products to be included in the WHO essential drug category. The relevance of several PDMPs products has been confirmed to be included in the WHO Essential Medicines [3].

The World Health Assembly resolution (WHA63.12) regarding "availability, safety, and quality of blood product" urges the member states of WHO to establish, implement and support a nationally coordinated blood and plasma program, managed efficiently and sustainably, in accordance with available resources, to achieve self-sufficiency [4]. Each government is responsible for

ensuring an adequate and equitable supply of plasma-derived products to prevent and treat the many serious conditions that occur worldwide [5].

The need for blood and blood products increases every year. However, most patients who need life-saving support with blood products still do not have access. There are several functions of each PDMPs utilized by the health service for clinical use, such as albumin for burn and hypoalbuminemia, Factor VIII to help Haemophilia type A, Antithrombin III for congenital deficiency. Most PDMPs are life-saving therapeutics medicines [2][6]. Therefore, it is crucial for all countries to have the national capacity to collect plasma components with optimal safety and quality in order to supply PDMPs adequately [7].

The progress in the plasma fractionation industry has stagnated after several decades [8]. On the other hand, the global need for PDMPs has increased [9]. WHO data recorded that 118.54 million blood donors were collected globally within a year. However, most blood donors collected from developing countries were not used to produce fractionated plasma products. Instead, they were wasted due to limited capacity for proper management [8]. Fulfilling domestic plasma products is still challenging for LMIC countries to reach. Various challenges need to be identified so that further efforts can be made to address them.

Utilization of international cooperation

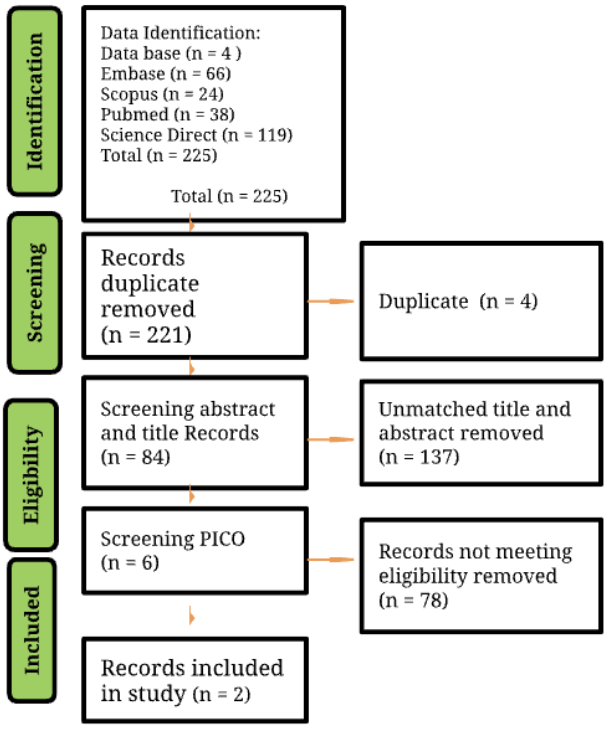
The gaps found will be a challenge for LMIC countries. The utilization of cooperation in fulfilling plasma drug products could be implemented one way through health diplomacy. The main goals of health diplomacy are a) better health security and population health; b) improved relations between states and a commitment of actors to work together to improve health; and b) achieve outcomes that are deemed fair and support the goals and increase equity [10]. Therefore, it is necessary to identify the strengths and weaknesses between relevant stakeholders at the national level and be able to continue by bringing this into negotiations with certain parties through various methods of international relations. This reflects what Anne Marie Slaughter states in her influential book on global policy networks: "Understanding 'domestic' issues in a regional or global context must become part of doing a good job" [11].

METHODS

A Systematic Literature Review or systematic planning is a research method that assists, evaluates, and interprets research relevant to a particular topic [12]. Details of activities are carried out by determining data search strategies and sources of information, selection of studies according to eligibility criteria and quality assessment, data synthesis, and data extraction. As a search strategy, the keywords used in the search were "plasma fractionation" AND "plasma derivative" AND "human" AND "industrial" OR "industrial" NOT "pharmacokinetics".Database used are Embase, Scopus, Pubmed, and ScienceDirect.

Literature selection was carried out to assess the quality and used the PRISMA method. The results of the literature selection are included in the PRISMA Flow Diagram in Figure 1. The article search results are entered into the Mendeley software for further filtering, such as eliminating duplicates. The screening results were entered into the Prisma method, which was carried out with details. Namely, out of a total of 221 articles, there were 4 articles of data duplication, then 137 had mismatched titles and abstracts. After reviewing, there were 78 whose data did not match the inclusion criteria, resulting in 2 selected journal data from the review results.

Figure 1 Prisma Flow Diagram



Eligibility criteria in this study include inclusion and exclusion criteria. The inclusion criteria in this study were 1) Literature in the form of scientific research journals/articles/expert opinions in terms of plasma products; 2) Embase Source, Scopus, Pubmed, and ScienceDirect, which are directly connected to the University of Indonesia; 3) Scientific journals/articles have open access; 4) Scientific journals use English; 5) Year of publication of scientific journals/articles

between 2012-2022; 6) Discussion in scientific journals includes challenges and strategies for implementing plasma fractionation in developing countries; 9) The research design is qualitative or descriptive. This review explores the extent to which research has overcome possible biases in design, implementation, and analysis with the JBI Critical Appraisal tool [13].

RESULTS

The development of plasma fractionation in LMIC countries needs to be improved to the problem of a lack of standardized blood management, which results in a lack of plasma quality and a large amount of wasted plasma. This is supported by the weak technology and facilities owned and the available resources. Lack of government attention can also be another inhibiting factor, so it is necessary to establish a policy that can strengthen the pace of development of domestic plasma fractionation in each LMIC country (Table 1).

Plasma products have strict and efficient regulations on each aspect of their production arrangement and clinical use in industrialized countries. The complexity of the technology and regulatory requirements are meant to be a barrier for LMIC countries to enter the field of plasma fractionation. This causes a shortage of plasma protein products, especially in LMIC countries, even though it is on the WHO list of essential medicines [3].

One of the major limitations due to the cost effectiveness of plasma fractionation technology is the equipment in large-scale orientations. However, this will result in the insufficient collection of plasma volume and substandard management, eventually leading to the wastage of plasma material [14]. The use of plasma for fractionation improved, and safe plasma products can be provided by agreements with established fractionators. But of course, the agreement will imply the appropriate quality specifications with which the extraction fractionator and the resulting plasma product must be licensed [3].

There are three main reasons for inhibiting plasma fractionation in LMIC countries, including (a) The quantity of high-quality plasma that meets international standards for fractionation is not sufficient as evidence of the need to build qualified domestic facilities; (b) The high capital costs required to design, build, validate, license and operate a GMP facility; and (c) a local team with an adequate understanding of biological processes and an inadequate level of technological background.

Based on the summary review found, the regulatory system is a must. It is tied principally, then goes to advance to others. First, how to gather the raw material appropriately, with good and sufficient quality. Practically, it is necessary to develop good manufacturing practices, disease screening, and appropriate storage systems to keep the quality of blood plasma and never neglect the cold chain system, developed as the first stage to reach the others.

Table 1. Summary review

Year	Author	Challenges	Strategy
2014	Thierry Burnouf, Jerard Seghatchian	1. A large amount of plasma is wasted due to unmet fractionation specification 2. Technological approach is still a serious problem for LMICs 3. Challenges in the transition process from contract to domestic fractionation	1. Development of GMP 2. The importance of technology transfer can be achieved by creating a collaboration 3. Develop a supportive regulation and other factors such as technology, finance, and resources
2020	Thierry Burnouf, Jean-Claude Fabere, Mirjana Radosevicf, Hadi Goubrang, Jerard Seghatchian	4. Inadequate quality of local plasma 5. Low ability to build facilities cause of economic situation 6. Lack of human resources 7. Lack of technology and facilities to support plasma fractionation 8. Immature regulatory system	4. Improve the regulatory system related to national blood collection 5. Improve the downstream technology 6. Capacity building by collaboration approach 7. Cooperate with skilled technology companies who understand biological product manufacturing 8. Assess the factors, evaluate the regulatory system, and develop

Secondly, the preparation for domestic plasma fractionation is possible with the facilitation and human resource, it should be prepared carefully. It also needs to prepare the financial resources to build the facilitation, States are also able to conduct a collaboration formulation that involves both the public and private sector or form a collective effort for support by utilizing the international organization membership, surely this part is also important, departed from wha WHA Resolution concern on how to developed availability, safety, and quality of blood to reach the access of the essential medicine, particularly blood products. Technology is also an important issue, LMICs have to build strategy into it by approaching the foreign fractionator that has been proven able to produce PDMPs and is keen to transfer the technology.

Third, the concern of how to absorb the local product to guarantee the continuity of its existence influences the progress of toll fractionation to be indirectly domestic fractionation. This is important so that slowly the stages of the plasma fractionation process in LMICs countries can be carried out, running independently as expected to achieve self-sufficiency of PDMPs drugs in their countries.

DISCUSSIONS

The fractionation plant should be designed with great care based on the core fractionation process of all products. Strictly controlled and monitored is needed to avoid the chance of downstream or cross-contamination risk should be done with working procedures. Considering that human plasma is susceptible, constant vigilance is required to maintain safety and thus requires compliance with quality control tests. If it cannot be guarded and continuously exposed, the threat of new, known, and unknown infectious agents exist [14].

Another approach to initiate gradual independent plasma fractionation would be implemented through a local mini-pool. However, this approach would be limited by high capital cost requirements. However, it would facilitate practical implementation and allow for a progressive and gradual increase in local expertise toward large-scale processing [3]. On fulfilling the PDMP, fractionation can be done through contract or domestic means. LMICs countries still have problems in providing fractionation facilities. So that a contract fractionation mechanism emerged, which has also been used by several LMIC countries, such as Iran [6], Thailand [15], and Morocco [16].

Contract fractionation as a suggestion

Currently, contract fractionation is a pragmatic method. However, the pressure for world needs continues to increase, so it is necessary to develop the plasma fractionation industry in LMICs to fulfill and access PDMPs needs which is also a manifestation of each country's pharmaceutical resilience. Technology transfer is crucial in implementing domestic plasma fractionation in LMIC countries. To overcome the problem of supply and product safety for PDMPs, it is recommended that LMICs need to involve industry in developed countries. Of course, this can only be done by fulfilling all the requirements and following the existing regulations. On the other hand, cooperation from bilateral or multilateral sectors such as WHO and other forums can be utilized to provide information, technology transfer, and capacity building according to the mandate of WHA resolution 63.12.

Contract plasma fractionation is an arrangement in which domestic plasma is provided to a fractionator licensed in a foreign country, and PDMPs are provided in return, according to predetermined terms for use within the country [17]. In connection with the economic and technological challenges associated with high capital investments requiring in-country fractionation facilities, plasma contract fractionation was an approach deemed reasonable for approval. However, strict supervision is needed from plasma suppliers and fractionators. Contract fractionation is considered pragmatic, but the possibility of benefit lies in the quality and safety of blood components by introducing the concept of Good Manufacturing Practices (GMP) [14].

Improving domestic policy in plasma fractionation

In contrast, technical, financial, and policy challenges must be considered in developing domestic fractionation facilities, that is highly regulated at the global level [14]. System development for increasing PDMP supply through contract fractionation and domestic for each country is different. Various factors need to be considered and pursued in stages at the national level. One of the main problems in developing countries is that the collected plasma usually unmet specifications for fractionation, and most of them are wasted. However, the situation has gradually improved since several blood components were included in the WHO's list of essential medicines. Government awareness is needed to support policies related to GMP to achieve quality and safety and increase product supply [14].

Health diplomacy

The role of diplomacy in health is vital. As health becomes an ever more critical element in foreign policy, security policy, development strategies, and trade agreements, new skills are needed to negotiate for health in the face of other interests. An increasing number of

health challenges can no longer be resolved at the technical level only, they require political negotiations and often need to involve a wide range of actors [18].

The “core global diplomacy” refers to government interactions, including policy implementation, advocacy, negotiation, intelligence, and issue-based diplomacy. Classical Westphalian interpretation classifies bilateral and multilateral as formal agreements to resolve disputes [19]. Bilateral negotiation involves negotiations between national representatives. This term is used in contract fractionation, but one thing should be assured both parties should get a win-win solution on this term. Transfer technology is important in developing plasma fractionation, and it could be the thing that should be considered the how and where of technology transfer.

Technology transfer is enhanced by stronger levels of patent protection while acknowledging the necessity of complementary factors such as infrastructure, effective government policies and regulations, knowledge institutions, access to credit and venture capital, skilled human capital, and networks for research collaboration. The three principal problems to be considered in disseminating the technology transfer are asymmetric information, market power, and externalities. In addition, uncertainty regarding the innovation's qualities and future input prices will complicate the adoption process. New technologies frequently challenge existing legal systems in new ways and foster the evolution of the law [20].

Besides the multilateral negotiation, LMICs should be able to work together to find collective commitment and support to build an agreement proffered in the multilateral forum, which has committed and believes that the access of the PDMP is part of SDGs target, equitable access to drugs, so no one left behind.

Multilateral concepts have many successes shown by creating ad-hoc diplomatic gatherings; G20 is one of the most famous and influential ad hoc today. In Asia, ASEAN could be the best multilateral diplomacy at the regional level that has succeeded in enhancing cooperation in providing an essential geopolitical platform for other Asian powers to meet and confer on neutral ground. Multilateral diplomacy proliferates and works well in specialized organizations like WHO [21]. In this context, WHO has developed guidance on increasing supplies of plasma-derived medicinal products in LMICs through the fractionation of domestic plasma.

Furthermore, maybe the continuation of efforts to make a resolution at the WHA, which could have been driven by LMICs regarding technical support and other capacity building in the implementation of plasma fractionation, considering that WHO already has cooperation with experts in this field, such as the International Society of Blood Transfusion. If it works, it definitely will cover the various deficiencies of the existing bilateral gaps.

CONCLUSION

The commitments of the LMICs state governments must be implemented in concrete form. Policy establishment and arrangements must be made and adapted to achieve pharmaceutical manufacturers capable of plasma fractionation. Not only paying attention to quality but also related to the management of blood products as commercial products with ethical values and strict regulations in their application.

The research findings could be a recommendation for the Governments of LMICs countries that wish to carry out domestic plasma fractionation to meet the needs of national PDMPs products. The policy design that contains arrangements must be balanced with efforts to increase the findings of factors that are still a weakness so that later the readiness to implement the fractionation implementation policy can run well.

Furthermore, other researchers may further analyze the cost-effectiveness of implementing plasma fractionation contracts compared to purchasing imported PDMP products. This analysis strengthens the recommendation that domestic fractionation will positively impact fulfilling access to national PDMPs in each LMIC country.

In particular, as Indonesia has developed plasma fractionation regulation as the self- sufficiency of blood products, contract plasma fractionation is an excellent choice to receive transfer technology gradually. However, it also reminds us that there are win-win solutions that limit and obstruct, so they cannot reach ultimately.

The result of this study can be a suggestion for all stakeholders, both policymakers and practitioners, to work together and bring this as the national interest, then negotiate in the form of health diplomacy in many multilateral fora. Collective commitment can be formed by initiating or joining other countries to fulfill existing gaps and realize blood product self-sufficiency to achieve the health transformation target.

REFERENCES

1. WHO. Blood safety and availability. 2022. Available from: [Website]
2. Grazzini G, Mannucci PM, Oleari F. Plasma-derived medicinal products: demand and clinical use. Blood Transfusion. 2013:11;2–5.
3. Burnouf T, Faber J-C, Radosevic M, Goubran H, Seghatchian J. Plasma fractionation in countries with limited infrastructure and low-/medium income: How to move forward? Transfusion and

Apheresis Science. 2020:59;102715.
4. Flanagan P. Self-sufficiency in plasma supply. ISBT Science Series. 2017:112;42–43.
5. WHO. Availability, safety and quality of blood products (WHA63.12). 2010. Available from: [Website]
6. Hosseini KM, Ghasemzadeh M. Implementation of plasma fractionation in biological medicines production. Iran Journal of Biotechnology. 2016:14;213–220.
7. Dhingra N. International challenges of self-sufficiency in blood products. Transfusion Clinique et Biologique. 2013:20;148–152.
8. Seghatchian J. The state of plasma fractionation in technologically disadvantaged countries and current perspectives on the classification and applications of platelet-derived bio-products used in regenerative medicine. Transfusion and Apheresis Science. 2020:59;102714.
9. Cheraghali AM, Abolghasemi H. Improving availability and affordability of plasma-derived medicines. Biologicals. 2010: 38;81–86.
10. WHO EMRO. Health diplomacy. WHO; 2023. [Website]
11. Kickbusch I, Silberschmidt G, Buss P. Global health diplomacy: The need for new perspectives, strategic approaches and skills in global health. Bulletin of World Health Organization. 2007:85;230–232.
12. Siswanto. Systematic review sebagai metode penelitian untuk mensintesis hasil-hasil penelitian. Buletin Penelitian Sistem Kesehatan. 2010:13.
13. JBI Critical Appraisal Tools | JBI; 2023. Available from: [Website]
14. Burnouf T, Seghatchian J. “Go no Go” in plasma fractionation in the world’s emerging economies: still a question asked 70 years after the COHN process was developed! Transfusion and Apheresis Science. 2014:51;113–119.
15. Charoonruangrit U, Rungpradubvong W, Witthayawiwat P, Chaiwong K. Thailand experience all the way from cryo, dryheated cryo, and domestic industrial factor VIII concentrate production. Vox Sang. 2020:115;44.
16. Lahjouji K. Plasma fractionation, the Moroccan experience. Vox Sang. 2016:111;10–11.
17. Rossi F. Oversight of contract plasma fractionation. 2021. Available from: [Website]
18. WHO EMRO. Global health needs global health diplomacy | Health diplomacy | Health topics. 2023. Available from: [Website]
19. Katz R, Kornblet S, Arnold G, Lief E, Fischer JE. Defining health diplomacy: Changing demands in the era of globalization. The Milbank Quarterly. 2011:89;503–523.
20. Johnson DKN, Lybecker KM. Challenges to technology transfer: a literature review of the constraints on environmental technology dissemination. SSRN Electron Journal. 2011;1–42.
21. Mahbubani K. The Asian 21st century. Springer Nature. 2022.