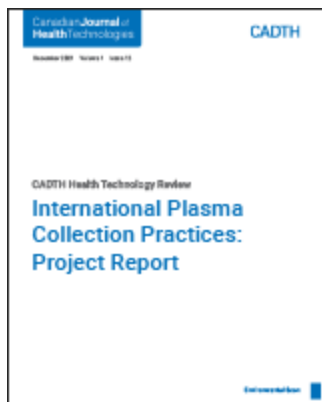




International Plasma Collection Practices: Project Report

CADTH Health Technology Review

Authors; Sirjana Pant, Rupinder Bagha, and Sarah McGill.

Ottawa (ON): [Canadian Agency for Drugs and Technologies in Health](#); 2021 Dec.

Report No.: ES0356

[Copyright and Permissions](#)

Acknowledgements: Christine Perras, Amanda Manoharan

Abbreviations

CBS

Canadian Blood Services

CHM

Commission on Human Medicines

CJD

Creutzfeldt-Jakob disease

CPR

Canadian Plasma Resources

EFS

French Blood Establishment (Établissement français du sang)

ES

Environmental Scan

HAV

Hepatitis A Virus

HBV

hepatitis B virus

HCV

hepatitis C

HEV

hepatitis E virus

H-Q

Héma-Québec

HTLV

human T-lymphotropic virus

Ig

immunoglobulin

IVIg

intravenous immunoglobulin

NHSBT

NHS Blood and Transplant

NIBTS

Northern Ireland Blood Transfusion Service

Nig

normal immunoglobulin

NZBS

New Zealand Blood Service

PDMPs

plasma-derived medicinal products

PPTA

Plasma Protein Therapeutics Association

Rho(D)Ig

Rho (D) Immunoglobulin

SCIg

subcutaneous immunoglobulin

SNBTS

Scottish National Blood Transfusion Service

WBS

Welsh Blood Service

Key Messages

- Plasma is used by pharmaceutical companies to make plasma-derived medicinal products (PDMPs). PDMPs are used to treat conditions such as immune deficiencies and bleeding disorders. Several PDMPs are included in the WHO Model Lists of Essential Medicines. According to the WHO, self-sufficiency driven by voluntary (non-remunerated) plasma

donations is an important national goal to ensure an adequate supply is secured to meet the needs of the population.

- Australia, New Zealand, the UK, the Netherlands, and France only allow public or not-for-profit sectors to collect plasma for fractionation. Each of the 5 countries have toll or contract agreements with 1 private commercial plasma fractionator to manufacture PDMPs from the plasma collected within their respective countries. None of these countries pay plasma donors. Donors are only permitted to donate every 2 weeks (24 to 26 times per year) in these 5 countries.
- Austria, the Czech Republic, Germany, and the US allow both public and non-for-profit sectors, as well as commercial private plasma collection centres, to operate in the country. Private, not-for-profit, or public plasma collection centres in these 4 countries offer monetary compensation and other in-kind incentives to plasma donors. While the Czech Republic limits plasma donation to every 2 weeks, a much higher frequency of donation is allowed in other countries; up to 50 times per year in Austria, 60 times per year in Germany, and more than 100 times per year in the US.
- Austria, the Czech Republic, Germany, and the US (which allow commercial private plasma collectors to operate and pay donors) are 100% self-sufficient in immunoglobulins. These 4 countries collect the most plasma, which is from paid donors. In 2017, Austria, the Czech Republic, Germany, and the US collected 75 litres per 1,000 people, 45 litres per 1,000 people, 36 litres per 1,000 people, and 113 litres per 1,000 people of plasma for fractionation, respectively. Countries that do not pay donors including Australia, New Zealand, the UK, the Netherlands, and France are dependent to some extent on US and European Union donors who are paid for the supply of plasma or imported PDMPs.
- The limited literature search conducted for the Environmental Scan did not identify publications on events of disease transmission through PDMPs manufactured from either paid or non-renumerated donors' plasma, the impact of plasma collection centres (including those that do or do not pay donors) on the collection of whole blood or other blood components, or the long-term costs associated with plasma self-sufficiency on the health care system.

Abstract

Plasma, collected from donors, is used to manufacture life-saving plasma-derived medicinal products (PDMPs). While the WHO promotes self-sufficiency in plasma supply from non-renumerated donors as a key national goal, Canada still relies heavily on plasma that is imported from paid US donors. The reliance on foreign plasma supply may lead to shortages as a result of market disruptions caused by events such as the COVID-19 pandemic. Hence, it is important for Canada to identify models to improve its self-sufficiency on plasma supply while ensuring the safety of both patients and donors. This Environmental Scan (ES) provides a summary of findings on the models used by international jurisdictions for plasma collection — from paid and non-renumerated plasma donors or a mix of both — to improve their self-sufficiency on the supply of plasma to manufacture PDMPs.

A limited literature search was conducted to inform the ES, including an internet search of relevant websites. Information was gathered on plasma supply models for the following 9 countries: Australia, New Zealand, the UK, the Netherlands, France, Austria, the Czech Republic, Germany, and the US.

Australia, New Zealand, the UK, the Netherlands, and France only allow public and non-for-profit sectors to collect plasma for fractionation. Each of these 5 countries have a contract with 1 private commercial plasma fractionator to manufacture PDMPs from the plasma collected within their respective countries. None of these countries permit monetary compensation to plasma donors. Austria, the Czech Republic, Germany, and the US allow public, non-for-profit sectors, and commercial private plasma collection centres to operate in the country. Private plasma collection centres pay the donors for their time and inconvenience. The allowed donation frequency is much higher in countries that permit monetary compensation to donors (up to more than 100 times per year) versus those that do not allow monetary compensation to donors (2 to 26 times per year). Countries that permit private sectors to collect plasma are self-sufficient on plasma supply for immunoglobulin (Ig), which is the most frequently consumed PDMP and the largest driver of the growth in PDMP use. Countries that do not permit private collection centres to operate rely to some extent on plasma from paid European Union (EU) or US donors. The limited literature search conducted for the ES did not identify publications on events of disease transmission through PDMPs manufactured from either paid or non-renumerated donors' plasma, the impact of plasma collection centres (including those that do or do not pay donors) on the collection of whole blood or other blood components, or the long-term costs associated with plasma self-sufficiency on the health care system.

Context

Plasma is the liquid in our blood that transports red and white blood cells, platelets, albumin, clotting factor, and proteins including antibodies called immune globulins. Plasma represents 55% of the total volume of the blood.¹ Plasma is used as life-saving therapies for trauma, burn, and shock patients, as well as people with severe liver disease or multiple clotting factor deficiencies. Plasma is also used by specialty pharmaceutical companies to manufacture PDMPs, which are biologic therapies solely derived from human biologic material — plasma. PDMPs are used for conditions such as immune deficiencies and bleeding disorders.^{2,3} Blood and blood components including plasma and several PDMPs (e.g., coagulation factor VIII, factor IX, immunoglobulins, anti-D immunoglobulin [Ig], anti-tetanus Ig, and anti-rabies Ig) are classified under the WHO Model List of Essential Medicines.⁴

Plasma for fractionation — simplified, the manufacture of PDMPs — can be collected as either “recovered plasma,” defined as plasma separated from a whole blood donation, or “source plasma,” which is collected directly from the donor using a plasmapheresis (apheresis) machine. Because the source plasma collection process only collects plasma and returns the remaining blood components to the donor at the time of donation, a much higher volume of plasma — up to 3 times more — can be collected from this method.^{1,5} A total of 85% to 90% of PDMPs are made from plasma collected as source plasma; that is, through the plasmapheresis process. While the collection of source plasma is increasing, the collection of recovered plasma appears to be stable to declining.⁶

The process of plasma collection is complex and labour- and time-intensive. Plasma collection and PDMP manufacturing process are regulated through distinct mechanisms to address their unique needs such as ensuring patient and donor safety.^{3,7-10} Whole blood and plasma are collected by public or non-profit sectors, as well as the commercial private sector (hereafter, the private sector). The private sector primarily collects source plasma to manufacture PDMPs.^{1,5} The majority of plasma collection centres are part of some plasma fractionators. The plasma collected is sold to the plasma fractionators to manufacture PDMPs.^{3,11-43} For the purposes of this ES, the term “plasma

fractionator” is used to refer to the biopharmaceutical industry that manufacture PDMPs. Plasma collection centres offer various incentives to donors for their time and inconvenience, which include but are not limited to, refreshments, in-kind gifts, travel allowance, paid day-off-from-work leave, and free physical check-ups. In addition, some countries also permit monetary compensation to donors. For the purposes of this ES, donors who receive such monetary compensations are referred as “paid donors.” While the private sector gives monetary compensation to plasma donors, the public or the not-for-profit sectors generally do not.^{1,5}

Héma-Québec (H-Q) and the Canadian Blood Services (CBS) collect and distribute blood and plasma and purchase PDMPs for patients across Canada. Commercial private sector plasma fractionators located in the US or European countries such as Switzerland manufacture PDMPs from the plasma collected by H-Q and CBS for use by Canadians.⁵ In 2019, CBS estimated Canada’s Ig self-sufficiency rate at 13.7%.^{5,44} The rest of the Ig output (86.3%), as well as other PDMPs used in Canada, are manufactured by contracted global plasma fractionators that collect their plasma from paid US donors.⁵ Canada’s Ig self-sufficiency rate has been steadily declining from 21% in 2015 followed by 18% in 2016, 17% in 2017, and 15% in 2018.^{5,44} Canada has the second-largest per capita utilization of Ig.⁴⁵

The commercial sector, albeit small, also operates in Canada (Saskatoon and Moncton) to collect plasma from paid donors. For more than 40 years, Prometic Life Sciences Inc. (now Liminal BioSciences) has been collecting plasma from paid donors in Winnipeg to manufacture Rho (D) immunoglobulins (Rho [D]) Ig for the prevention of rhesus (Rh) isoimmunization, or Rh disease, of the newborn for use in Canada and elsewhere. Canadian Plasma Resources (CPR) also collects plasma from paid donors in Saskatoon and Moncton, which is sold to Biotest, a European fractionator.⁵ CPR has plans to open new sites in Edmonton and Calgary in the fall of 2021.⁴⁶

The use of plasma to manufacture PMDPs has grown steadily in Canada with increasingly sophisticated usage of existing and new products. A challenge for decision-makers is to ensure adequate plasma supply to meet the needs of patients with the goal of achieving self-sufficiency. One central issue impacting these discussions is resistance toward the payment of donors; either through the public or not-for-profit plasma collection centres or by permitting private plasma collection centres to operate in the country. This issue is accompanied by ethical concerns about the commodification of human body parts and concerns about the safety of products made from paid donors.^{1,5,44} Given the growing global dependence on the EU and the US for source plasma, strategies to protect the supply of plasma and PDMPs in Canada require ongoing attention.

Objectives

This ES provides information on the models used by international jurisdictions for plasma collection from paid and non-renumerated donors, or a mix of both, to improve their self-sufficiency on the supply of plasma for fractionation (that is, the manufacturing of PDMPs). The ES will provide information on the following:

- blood operators and plasma fractionators, and plasma centres
- donor status
- dependency on other jurisdictions and associated risks
- plasma products manufactured

- safety issues and measures
- legislation or policies.

The ES is focused on the supply of plasma for fractionation only; that is, plasma used by pharmaceutical companies to manufacture PDMPs. Therefore, the ES excludes information on fresh-frozen plasma used in hospital settings. This ES does not provide information on the supply of whole blood or other blood components such as platelets. Information on the optimal use, efficacy, and safety of PDMPs to treat patients, and utilization data, are outside the scope of the ES. Any difference in safety measures employed to ensure donors and patient safety between paid and non-renumerated plasma donation models are also described. The ES does not discuss viral or bacterial screening or neutralizing technologies in the plasma supply or its effectiveness. The ethical concerns associated with paying for a body part is also beyond the scope of this ES.

Research Questions

The following research questions were addressed:

Blood Operators and Plasma Fractionators

1. What organization(s) is (are) responsible for collecting plasma within each country?
2. What organization(s) is (are) responsible for producing plasma-derived medicinal products within each country?

Dependency on Other Jurisdictions and Associated Risks

3. Which countries depend on other countries/jurisdictions for their plasma supply?
4. On which countries/jurisdictions are they dependent on?
5. What are the risks of depending on other countries/jurisdictions for plasma supply?

Type of PDPs Produced

6. What are the types of plasma-derived medicinal products manufactured by each country?

Dedicated Plasma Centres (Private Versus Public)

7. What are the types of plasma collection centres (private, public, or both) allowed to operate in each country?

Plasma Donor Status

8. For each type of plasma collection centre, are plasma donors compensated?
9. For each type of plasma collection centre, what are the personal donor requirements for donating blood (e.g., identification, permanent address)?

Legislative or Regulatory Framework for Compensation of Donors and Any Restrictions on the Export/Import of Plasma

10. For each country, what is the regulatory framework or legislation for compensating donors?
11. For each country, what is the regulatory framework or legislation for importing plasma?

Long-Term Cost Savings/Premiums of Self-Sufficiency to the Health Care System

12. What are the cost implications (savings or premiums) of having a self-sufficient plasma collection system?

Safety of Products From Private Plasma Collection Sites and Other Countries

13. What are the safety concerns associated with private plasma collection sites?

14. What are the safety concerns with using plasma collected in another country or jurisdiction?

15. What safety measures are required to ensure the integrity of the supply from other countries?

16. What safety measures are required to ensure the integrity of the supply from private plasma collection sites?

Safety of Products From Paid Donations

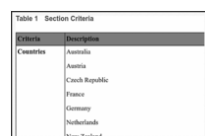
17. What are the safety concerns associated with paid plasma collection?

Impact of Compensated Plasma Donations on Voluntary Blood Donation Rates

18. What is the impact of compensated plasma collection on voluntary blood donation rates?

Methods

The findings of this ES are based on information obtained from 9 countries and topics outlined in Table 1.



Criteria	Description
Australia	
Austria	
Czech Republic	
France	
Germany	
Netherlands	
United Kingdom	

Table 1

Section Criteria.

Literature Search

A limited literature search was conducted by an information specialist on key resources including MEDLINE through Ovid, Scopus, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were plasma and plasma-derived products and supply, remuneration, paid collection, self-sufficiency, cost, or safety. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population and comments, newspaper articles, editorials, and letters were excluded. The search was limited to English-language documents published between January 1, 2010 and April 15, 2021.

Regular database and grey literature search updates were run until May 21, 2021. Information meeting the selection criteria of the review and identified in the alerts were incorporated in the summary of findings of the ES.

These searches were supplemented by reviewing bibliographies of key papers.

Findings

The ES presents a summary of the findings relating to plasma collection models. Further details on plasma collection and fractionation in each country are provided in [Appendix 1: Country Profiles](#).

Blood Operators and Plasma Fractionators, and Plasma Centres

Australia, New Zealand, the UK, the Netherlands, and France only allow public and non-for-profit sectors to collect plasma for fractionation. These 5 countries may also import plasma if the amount collected within the country is not sufficient to meet local demands. Each of these 5 countries have arrangements with 1 private commercial plasma fractionator to manufacture PDMPs from the plasma that is collected within the country and plasma that is imported.^{3,11-43}

Austria, the Czech Republic, Germany, and the US allow public and non-for-profit sectors, as well as private plasma collection centres, to operate. These 4 countries have private plasma collection centres operating with more than 15 centres in Austria, more than 25 in the Czech Republic, more than 85 in Germany, and more than 900 in the US. All of the 4 countries are self-sufficient in plasma supply.^{3,11-43} However, some countries (e.g., the US) may rely on commercial fractionators located outside the country to manufacture PDMPs, which are imported into the US to meet local needs.⁴¹

Countries with the domestic capacity to fractionate plasma for the production of PDMPs include Australia, the UK, the Netherlands, France, Austria, Germany, and the US.⁴⁷ Of note, the plasma fractionation industry in North America, Europe, Australia, and New Zealand is dominated by the global biopharmaceutical industry.⁴⁸ Among the countries studied for this ES, only the commercial plasma fractionator LFB in France is solely state-owned.⁴⁹ The remaining countries including Australia, the UK, the Netherlands, Austria, Germany, and the US have only privately owned fractionation plants. Australia, New Zealand, the UK, the Netherlands, and France have toll fractionation agreements for the import of PDMPs made from domestic plasma supplies. In circumstances where there is a surplus supply of plasma, the US, France, and the Netherlands have the capacity to engage in contract fractionation agreements with not-for-profit entities or other countries. The WHO defines a toll fractionation agreement as “an arrangement by which domestic plasma is processed by a fractionator licensed in a foreign country and PDMPs from this plasma are provided in return, according to predetermined contractual terms, for use within the country” (page XI).⁴⁷ Contrastingly, a contract fractionation agreement is defined as “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” (page IX). Through toll fractionation, all products manufactured from the supplied domestic plasma is returned to the country from which the plasma originates. However, with a contract fractionation agreement, different arrangements for the products manufactured can be made. For example, plasma can be provided in exchange for products from the fractionator. Given that the details of these toll and contract manufacturing agreements are proprietary, further information pertaining to the specific conditions within these agreements was not available.⁴⁷

France is the only country that restricts the importation of PDMPs from plasma acquired through paid donors.⁴⁹ LFB in France holds the exclusive right to fractionated plasma resulting from voluntary blood donations collected by the French Blood Establishment.⁵⁰ LFB sells the PDMP derived from French plasma on the domestic market. In addition, both France and the Netherlands have an open domestic market for PDMPs, which allows hospitals to purchase their own PDMPs registered for sale in that country from any desired commercial manufacturer.⁵¹ French hospitals are therefore free to purchase any brands of PDMPs registered for sale in France and do not

necessarily have to purchase LFB products.⁵¹ It is reported that the use of PDMPs from paid donors in French hospitals is close to 50%.⁵²

While the UK has a fractionation plant in the country, to date it has purchased paid plasma primarily from the US because of concerns over the spread of Creutzfeldt-Jakob disease (CJD) in the UK population. Up until February 2021, the UK had a restriction on the collection of plasma because of the risk of CJD transmission. However, the ban is now lifted, and England and Scotland have started collecting plasma for fractionation. England will identify a private commercial fractionator in late 2021 to manufacture PDMPs from the plasma collected in the country.^{18,20-23}

Table 2 presents information on plasma collection centres and plasma fractionators by country and restriction on import and export.

Table 2 Plasma Collection Centres and Plasma Fractionators

Country	Public, not-for-profit, or private blood collection	Type of operation	Restrictions on import and export
Australia	Not-for-profit (Lifeline)	CBL	Most plasma is manufactured by Australian Red Cross

Table 2

Plasma Collection Centres and Plasma Fractionators, and Restrictions on Import and Export.

Donor Compensation Status

While legislation governing the collection of blood and blood components in most countries stresses the role of voluntary non-remunerated plasma donations as the primary measure to solicit plasma donations, the application of this principle varies across countries.⁵⁷ For instance, legislation and policies governing public and not-for-profit plasma collectors in Austria, France, Germany, the UK, and Australia prohibit any form of payment to plasma donors.^{5,49,58-61} However, the private plasma collectors in these countries (with the exception of the UK, France, and Australia) provide some incentives including monetary compensation to plasma donors. Among the incentives outlined in Table 3, it is unclear which are permissible within the principle of voluntary non-remunerated donations and which are considered a form of compensation. This suggests that these countries have varying interpretations relating to the principle of voluntary non-remunerated donors. This finding is consistent with the observations of Health Canada’s expert panel report on Protecting Access to Immune Globulins for Canadians, which highlights that the definition of “volunteer” is shifting and “in many instances [the incentives provided to plasma donors] have a value equivalent or even greater to what would be considered payment in Canada and other jurisdictions.”⁵

Donors are only permitted to donate every 2 weeks (24 to 26 times per year) in Australia, New Zealand, and France; these are the same countries that only permit public and not-for-profit plasma collection centres. With the exception of the Czech Republic, which also allows plasma donation every 2 weeks, the frequency of donation is much higher in the other 3 countries that allow private plasma collectors to operate: up to 50 times per year in Austria, up to 60 times per year in Germany, and more than 100 times per year in the US. The amount of plasma collected ranges from 625 mL to 850 mL per donation and in some countries the amount collected is proportional to the weight of the person. Donors must be older than 18 years of age to donate plasma, however the upper age limit ranges from 60 years to 75 years of age. Depending on the country, the lower weight limit ranges are from 50 kg to 55 kg. All private plasma collectors require donors to present valid photo identification. Other requirements of private plasma collectors include proof of health insurance in the Czech Republic; a blood donation card in Germany; and a social security number or visa, border crossing card, and proof of local residency in the US.^{1,3,21,34,36,40,42,43,62-101}

Table 3 presents information on the status of monetary compensation, donation frequency, and the amount of plasma collected per donation.

Table 4 presents information on age and weight requirements, as well as requirements for identification.

Table 3 Monetary Compensation, Donation Frequency, and

Country	Monetary compensation status	Example of monetary compensation amount	Example of frequency
Australia	Uncompensated	None identified	None identified
New Zealand	Uncompensated	None identified	None identified

Table 3

Monetary Compensation, Donation Frequency, and Plasma Collected Per Donation.

Table 4 Donor Requirements — Age and Weight, Identification Centres, Only)

Country	Age (years)	Weight (kg)
Australia	18 to 75	> 50
New Zealand	18 to 60	> 50
UK ⁴	18 to 60	NA
Netherlands	18 to 65	> 55
France	18 to 60	> 55
Austria	18 to 60 (not to 64 only)	50 to 100 with a BMI < 40

Table 4

Donor Requirements — Age and Weight, Identification (for Private Plasma Collection Centres, Only).

Dependency, Associated Risk, and PDMPs Manufactured

The market for PDMPs is primarily driven by Ig. Only countries that allow private plasma collectors to operate and allow paid donors are 100% self-sufficient on Ig. The other countries including Australia, New Zealand, the UK, France, and the Netherlands that do not allow paid donors are dependent on US and EU donors, who are paid. These countries leverage toll fractionation agreements with commercial fractionators to fulfill domestic needs, as demonstrated in Table 2.

In 2019 to 2020, Australia, New Zealand, and the UK imported 54%,12%, and 100% of plasma for fractionation, respectively, to manufacture Ig. While the Netherlands was also an importer of plasma for Ig, the percentage imported is unknown. Hospitals in France use almost 50% of imported PDMPs manufactured from paid plasma donors. In 2017, Austria, the Czech Republic, Germany, and the US collected 75 litres of plasma per 1,000 people, 45 litres per 1,000 people, 36 litres per 1,000 people, and 13 litres per 1,000 people for fractionation, respectively.^{1,3,5,13,20,37,39,41,52,66,70,102-107}

The global plasma market is experiencing growing demands driven largely by the need for Ig and an overall decline in plasma donations due to the COVID-19 pandemic. It is estimated that plasma collection has decreased by 20% in 2020 because of the pandemic.^{55,108-111} Media reports attribute the decline to several factors such as social distancing requirements, donor reluctance due to the fear of contracting the virus, lack of child care and transportation, as well as border closures preventing many who would come up from Mexico to donate.^{108,112} The global market for Ig therapy is growing at the rate of 6% to 8% annually.¹⁰⁷ According to WHO, self-sufficiency driven by voluntary (non-remunerated) plasma donations is an important national goal to ensure there is an adequate supply secured that meets the needs of the population.⁴ However, there is a significant geographical imbalance in the supply of plasma. As such, very few countries collect enough plasma to meet the needs of their populations. Many countries rely on the US and on European countries that allow plasma donors to be paid for the supply of plasma to manufacture PDMPs.^{1,3,5,107} Approximately 65% of the global plasma supply is collected in the US.¹⁰⁷ More than 55% of plasma collected in Europe was contributed collectively from Germany, Austria, the Czech Republic, and Hungary, which permit monetary compensation to plasma donors. Dependency on a few countries may present a challenge for plasma supply and a subsequent shortage in the event of a market disruption. So saying, Ig therapies are ranked as the third most-

frequent medicinal product facing shortages in the EU.¹⁰⁷ In 2019, Canada also reported an Ig shortage. Experts have warned of the risk of supply interruptions due to rising costs driven by international competition, especially as demand for Ig is increasing in emerging markets.^{1,55,108-111}

Table 5 presents information on the amount of plasma collected in various countries and self-sufficiency in Ig.

Table 5 Plasma Collected in Countries and Self-Sufficiency

Country	Plasma collected within the country for the treatment	Is treatment
Australia	600 tons of plasma (2019-2020), annual growth rate 4.7% (2019-2020)	7.01 million g nationally (2019-2020), annual growth rate 4.7% (2019-2020)
New Zealand	77,000 units (2019-2020)	90 g/1,000 people (2019-2020), annual growth rate 10% in 1970s (later stable) (2019)

Table 5
Plasma Collected in Countries and Self-Sufficiency in Immunoglobulin.

Safety Issues and Measures

There was no evidence in the limited literature search of the ES of any events of disease transmission through PDMPs manufactured from paid or voluntary (non-renumerated) donors’ plasma. In Canada, there have been “no confirmed cases of disease transmitted through PDMPs in over two decades”(page 47).⁵

Plasma collection centres (public, not-for-profit, and private) screen donors by conducting a medical interview and performing physical health checks. Donated plasma is tested for HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), and syphilis. Depending on the jurisdiction, test for hepatitis A virus (HAV), hepatitis E virus (HEV), human T-lymphotropic virus (HTLV) 1/2, human parvovirus B19, West Nile virus, and Chagas disease are also conducted.^{7,62,65,69-71,79,81,90,99-101,113,114}

Because of the risk of CJD, countries such as Australia, France, and New Zealand do not accept plasma donations from people who have lived in the UK at certain periods of time.^{67,80,115}

All countries use legislative instruments and regulations to ensure donor health and product quality.¹¹⁶⁻¹²⁰ This includes pre-market assessments and testing and auditing measures for plasma, plasma products, and manufacturers.

The plasma collection and fractionation industry and associations have also established voluntary safety standards to reduce potential relevant transfusion-transmitted infections’ (RTTI) contamination of source plasma, and to promote donor health. These include PPTA’s International Quality Plasma Program (IQPP) that is “focused on improving the quality of a facility’s donors, and its plasma collection operations” (page 10).⁷ Another such standard is the Quality Standards of Excellence, Assurance and Leadership (QSEAL) program, which has established “in-process testing for Parvovirus B19, the use of Nucleic Acid Amplification Technology (NAT) screening at the donation or pool level, and a Viral Marker Standard whereby a source plasma center must not exceed a national standard for positive RTTI test results or lose their industry IQPP certification” (page 10).⁷

Impact of Paid Donation

The limited literature search conducted for the ES did not identify any studies on whether the opening of plasma collection centres (both paid or non-renumerated) resulted in a decrease in the collection of whole blood or other blood components..

Cost Implication

The limited literature search conducted for the ES did not identify any studies that investigated the long-term impact of self-sufficiency to a health care system.

Conclusions and Implications for Decision- or Policy-Making

Canada's security of plasma and supply of PDMPs is threatened by the increasing demand in plasma products, the ongoing reliance on the US to fulfill supply gaps, and a decreasing donor base. It is essential for Canada to identify models to improve its self-sufficiency in plasma supply while addressing the factors that are influencing the growing demand for PDMP needs and ensuring the safety of the patients and donors.

Emerging international practices aimed at protecting the security and supply of plasma and PDMPs vary across jurisdictions. These variations are apparent in different models of plasma collection that involve either paid and/or non-remunerated donors, rates of donor frequency, prevalence of private and/or public collection facilities, and capacity for national fractionation of plasma, among others.

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has also emphasized a need to re-imagine these existing practices during heightened patterns of demand and reductions in donation rates.

The utilization of PDMPs provides life-enhancing and life-sustaining treatments for many patients with chronic conditions such as autoimmune deficiencies and hemophilia. Planning to ensure the adequate and efficient supply of plasma and PDMPs remains a complex issue involving collaboration among multiple levels of stakeholders, recognition of global and regional trends in demand and supply of plasma, debates concerning ethical principles related to the appropriateness of compensating plasma donors, and global market structures that influence importation and exportation activities. The security and safety of plasma and PDMP supply within Canada remains an important concern for decision-makers as they ensure patient needs continue to be met and that policies are developed to meet real needs within an ever-changing health care landscape.

Gaps in evidence were identified in that the limited literature search of the ES did not retrieve information on events of disease transmission through PDMPs manufactured from either paid or non-renumerated donors' plasma, the impact of plasma collection centres (including those that do or do not pay donors) on the collection of whole blood or other blood components, or the long-term costs associated with plasma self-sufficiency on the health care system

References

1. Jaworski P. Bloody well pay them: the case for voluntary remunerated plasma collections. Washington, D.C.: Niskanen Center; 2020: <https://www.niskanencenter.org/bloody-well-pay-them-the-case-for-voluntary-remunerated-plasma-collections/>. Accessed 2021 May 15.
2. American Red Cross. The importance of plasma in blood. 2021; <https://www.redcrossblood.org/donate-blood/dlp/plasma-information.html>. Accessed 2021 May 22.
3. Kluszczynski T, Rohr S, Ernst R. Key economic and value considerations for Plasma-Derived Medicinal Products (PDMPs) in Europe. (*White paper commissioned by the Plasma Protein Therapeutics Association (PPTA)*). Baarn (Netherlands): Vintura; 2020: https://www.vintura.com/wp-content/uploads/2020/03/White-paper-key-economic-and-value-considerations-for-plasma-derived-medicinal-products-PDMPs-in-Europe_Vintura-and-PPTA.pdf. Accessed 2021 May 15.
- 4.

WHO. Self-sufficiency in blood and blood products based on voluntary non-remunerated blood and plasma donations. [2011?]; https://www.who.int/bloodsafety/transfusion_services/self_sufficiency/en/. Accessed 2021 May 22.

5. Health Canada. Protecting access to immune globulins for Canadians: final report of the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada. Ottawa (ON): Health Canada; 2018: <https://www.canada.ca/en/health-canada/programs/expert-panel-immune-globulin-product-supply-related-impacts-canada/protecting-access-immune-globulins-canadians.html>. Accessed 2021 Jun 2.
6. Hartmann J, Klein HG. Supply and demand for plasma-derived medicinal products - a critical reassessment amid the COVID-19 pandemic. *Transfusion*. 2020;60(11):2748-2752. [PMC free article: PMC7460929] [PubMed: 32856742]
7. Weinstein M. Regulation of plasma for fractionation in the United States. *Annals of Blood*. 2018;3.
8. Bundesamt für Sicherheit im Gesundheitswesen [Austrian Federal Office for Safety in Health Care]. Plasma derived products. 2021: <https://www.basg.gv.at/en/companies/medicinal-products/plasma-derived-products#c13999>. Accessed 2021 May 22.
9. Bundesamt für Sicherheit im Gesundheitswesen [Austrian Federal Office for Safety in Health Care]. FAQ - human plasma for fractionation. 2021; <https://www.basg.gv.at/en/inspections/gmp/-gdp/faq-humanplasma-fraktionierung>. Accessed 2021 May 22.
10. European Medicines Agency. Guideline on plasma-derived medicinal products. EMA/CHMP/BWP/706271/2010. London: EMA; 2011: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-plasma-derived-medicinal-products_en.pdf. Accessed 2021 May 22.
11. National Blood Authority Australia. National Blood Authority homepage. 2021; <https://www.blood.gov.au/>. Accessed 2021 May 15.
12. Commonwealth of Australia Department of Health. What we're doing about blood and blood products. 2020; <https://www.health.gov.au/health-topics/blood-and-blood-products/what-were-doing-about-blood-and-blood-products>. Accessed 2021 May 15.
13. National Blood Authority Australia. Overview: ensuring supply. 2021; <https://www.blood.gov.au/ensuring-supply>. Accessed 2021 May 15.
14. National Blood Authority Factsheet: Supply of plasma derived and recombinant blood products. Canberra: National Blood Authority Australia; 2020: <https://www.blood.gov.au/system/files/Supply-of-Plasma-Derived-and-Recombinant-Blood-Products-Factsheet.pdf>. Accessed 2021 May 15.
15. New Zealand Blood Services. About NZBS: What we do. 2021; <https://www.nzblood.co.nz/about-nzbs/what-we-do/>. Accessed 2021 May 16.
16. New Zealand Blood Services. Distribution and supply of plasma derived fractionated blood products and recombinant products in New Zealand. Auckland: New Zealand Blood Services; 2020: <https://www.nzblood.co.nz/assets/Transfusion-Medicine/PDFs/160P002.pdf>. Accessed 2021 May 16.
17. European Blood Alliance. United Kingdom. [2021?]; <https://europeanbloodalliance.eu/country/united-kingdom/>. Accessed 2021 May 12.
18. Medicines and Healthcare products Regulatory Agency (MHRA). Critical risk assessment report: use of UK plasma for the manufacture of immunoglobulins and vCJD risk. London: Government of UK; 2020: <https://www.gov.uk/government/publications/critical-risk-assessment-report-use-of-uk-plasma-for-the-manufacture-of-immunoglobulins-and-vcjd-risk>. Accessed 2021 May 21.
- 19.

Sanquin Plasma Products. About. 2021; <https://www.plasmaproducts.com/about>. Accessed 2021 May 18.

20. NHS Blood and Transplant. First blood plasma for medicines donations begin. 2021; <https://www.nhsbt.nhs.uk/news/first-blood-plasma-for-medicines-donations-begin/>. Accessed 2021 May 12.
21. NHS Blood and Transplant. What is plasma used for? 2021; <https://www.blood.co.uk/why-give-blood/how-blood-is-used/blood-components/what-is-plasma-used-for/>. Accessed 2021 May 12.
22. Scottish National Blood Transfusion Service. Plasma for medicine: an update. 2021; <https://www.scotblood.co.uk/news/plasma-for-medicine-an-update/>. Accessed 2021 May 12.
23. Scottish Government. Blood plasma supply changes. Edinburgh: Scottish Government; 2021; <https://www.gov.scot/news/blood-plasma-supply-changes/>. Accessed 2021 May 12.
24. Sanquin. The story of Sanquin. [2021?]; <https://www.sanquin.nl/en/about-sanquin/the-story-of-sanquin>. Accessed 2021 May 18.
25. European Blood Alliance. France. [2021?]; <https://europeanbloodalliance.eu/country/france/>. Accessed 2021 May 12.
26. Etablissement français du sang [French Blood Establishment]. Objectives and performance contract. Saint-Denis (France): EFS; 2015: https://re7.efs.sante.fr/sites/instit/files/COP/EFS_COP2015-2018_EN.pdf. Accessed 2021 May 22.
27. LFB Biomedicaments S.A. Une société anonyme à capitaux majoritairement publics. 2021; <https://www.groupe-lfb.com/le-groupe/gouvernance/>. Accessed 2021 May 22. French.
28. Österreichisches Rotes Kreuz [Austrian Red Cross]. Ihre Blutspende: die häufigsten Fragen schnell beantwortet. 2021; <https://www.rotekreuz.at/ich-will-helfen/faqs-blutspende>. Accessed 2021 May 5. German.
29. PlasmaVita. VEREINBAREN SIE IHREN WUNSCHTERMIN. 2021; <https://plasmavita.at/#important-info>. Accessed 2021 May 5. German.
30. Plasma Protein Therapeutics Association (PPTA). Find a Donor Center. 2020; <https://www.donatingplasma.org/donation/find-a-donor-center>. Accessed 2021 May 5.
31. Bohonek M. The blood crisis policy in the Czech Republic. *Worldwide Military Medicine*. 2015. <https://military-medicine.com/article/3143-the-blood-crisis-policy-in-the-czech-republic.html>. Accessed 2021 May 5.
32. Plasma Protein Therapeutics Association (PPTA). Current members. 2020; <https://www.pptaglobal.org/about-us/current-members>. Accessed 2021 May 5.
33. Plasma Place. O PLASMA PLACE. [2021?]; <https://www.plasmaplace.cz/o-plasma-place/>. Accessed 2021 May 5. Czech.
34. UNICAPlasma. Jak se stát dárce. 2021; <https://www.unicaplasma.cz/jak-se-stat-darcem/>. Accessed 2021 May 5. Czech.
35. Sanaplasma. PROČ DAROVAT KREVNÍ PLASMU? 2020; <https://www.sanaplasma.cz/>. Accessed 2021 May 5. Czech.
36. Cara Plasma. Jak probíhá odběr. 2021; <https://www.caraplasma.cz/jak-probiha-odber>. Accessed 2021 May 5. Czech.
37. Moog R. The plasma supply in Germany. *Transfus Apheresis Sci*. 2019;58(6):102668. [PubMed: 31753775]
38. European Blood Alliance. Germany. [2021?]; <https://europeanbloodalliance.eu/country/germany/>. Accessed 2021 May 12.
39. Wetzl A. Interview with Dr. Franz Weinauer, Medical Director, Blood Donation Service of the Bavarian Red Cross. *The Source*. 2018(Fall). <https://www.pptaglobal>

- .org/images/source/2018/FALL/4._Interview_w_Dr._Franz_Weinauer.pdf. Accessed 2021 May 10.
40. DRK-Blutspendedienste. Die plasmaspende. 2021; <https://www.drk-blutspende.de/informationen-zur-blutspende/die-plasmaspende.php>. Accessed 2021 May 5.
 41. Penrod J. Plasma supply in the United States. *Transfus Apheresis Sci.* 2020;59(5):102931. [PubMed: 33071195]
 42. American Red Cross. Types of blood donations. 2021; <https://www.redcrossblood.org/donate-blood/how-to-donate/types-of-blood-donations.html>. Accessed 2021 May 5.
 43. America's Blood Centers. Membership directory. 2021; <https://americasblood.org/membership/membership-directory/>. Accessed 2021 May 8.
 44. Canadian Blood Services. Annual report 2019–2020. Ottawa: Canadian Blood Services; 2020: <https://annual2020.blood.ca/pdfs/cbs-ar2020-en.pdf#page=14>. Accessed 2021 May 2.
 45. Farrugia A, Grazzini G, Quinti I, Candura F, Profili S, Liumbruno GM. The growing importance of achieving national self-sufficiency in immunoglobulin in Italy. The emergence of a national imperative. *Blood Transfus.* 2019;17(6):449-458. [PMC free article: PMC6917530] [PubMed: 31846609]
 46. CBC News. Pay-for-plasma collection coming to Alberta by end of the year. 2021 Feb 14; <https://www.cbc.ca/news/canada/edmonton/pay-for-plasma-collection-coming-to-alberta-by-end-of-the-year-1.5911519>. Accessed 2021 Jun 15.
 47. WHO. Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma. Geneva: World Health Organization; 2021: <https://apps.who.int/iris/handle/10665/340171>. Accessed 2021 May 31.
 48. Plasma Protein Therapeutics Association (PPTA). Interactive map. 2021; <https://prezi.com/view/hXBhxDEIo8R2cavcdulK/>. Accessed 2021 May 5.
 49. Code de la santé publique [France Public Health Code]. Chapitre Ier: Collecte, préparation et conservation du sang, de ses composants et des produits sanguins labiles. Article L1221-3. [Chapter 1. Collection, preparation and storage of blood, its components and labile blood products. Article L1221-3.]. Paris: Légifrance; 2016: https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000033282026. Accessed 2021 May 18. French.
 50. Code de la santé publique [France Public Health Code]. Chapitre IV: Fabrication et distribution en gros. Article L 5124-14. Paris: Légifrance; 2016: https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000033282026. Accessed 2021 May 18. French.
 51. WHO. Towards self-sufficiency in safe blood and blood products based on voluntary non-remunerated donation. Global status 2013. 2013: <http://www.transfusion.ru/2014/02-26-2.pdf>. Accessed 2021 May 18.
 52. Garraud O, Martinaud C. The plasma supply in France. *Transfus Apheresis Sci.* 2019;58(4):358-362. [PubMed: 31253561]
 53. National Blood Authority Australia. Plasma and recombinant product procurement. 2021; <https://www.blood.gov.au/plasma-and-recombinant-product-procurement>. Accessed 2021 May 19.
 54. New Zealand Blood Service. Annual statement of performance expectation 1 July 2019 – 30 June 2020. Auckland: NZBS National Office; 2020: <https://www.nzblood.co.nz/assets/About-NZBS/PDFs/NZBS-SPE-for-2019-20-FINAL-30-May-2020.pdf>. Accessed 2021 May 19.
 55. Government of UK. Ban lifted to allow UK blood plasma to be used for life-saving treatments. 2021; <https://www.gov.uk/government/news/ban-lifted-to-allow-uk-blood-plasma-to-be-used-for-life-saving-treatments>. Accessed 2021 May 12.
 56. U.S. Food and Drug Administration. Import for export overview. 2021; <https://www.fda.gov/industry/import-basics/import-export-overview>. Accessed 2021 May 31.
 - 57.

European Commission Staff Working Document, on the implementation of the principle of voluntary and unpaid donation for human blood and blood components as foreseen in Directive 2002/98/EC on setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. European Commission; 2016: https://ec.europa.eu/health/sites/default/files/blood_tissues_organ/docs/swd_2016_130_en.pdf. Accessed 2021 May 17.

58. Bundesministerium der Justiz und für Verbraucherschutz [Federal Ministry of Justice and Consumer Protection Germany]. Gesetz zur Regelung des Transfusionswesens (Transfusionsgesetz - TFG) [German Transfusion Act]. 1998: <https://www.gesetze-im-internet.de/tfg/TFG.pdf>. Accessed 2021 May 18. German.
59. Gesamte Rechtsvorschrift für Blutsicherheitsgesetz 1999, Fassung vom 05.08.1999. Vienna (Austria): Rechtsinformationssystem des Bundes (RIS) [Legal Information System of the Republic of Austria]; 1999: <https://www.ris.bka.gv.at/GeltendeFassung/Bundesnormen/10011145/BSG%201999%2c%20Fassung%20vom%2026.05.2021.pdf>. Accessed 2021 May 18. German.
60. Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. Guidelines for the Blood Transfusion Services in the United Kingdom, 8th edition. London: TSO (The Stationery Office); 2013: <https://www.transfusionguidelines.org/red-book>. Accessed 2021 Jun 2.
61. National Blood Authority Australia. National Blood Agreement. Canberra: National Blood Authority Australia; 2002: <https://www.blood.gov.au/system/files/documents/nba-national-blood-agreement.pdf>. Accessed 2021 May 18.
62. Australian Red Cross LifeBlood. Selection of blood donors. 2021; https://transfusion.com.au/blood_basics/selection. Accessed 2021 May 15.
63. Slonim R. Life-saving Australian heroes should be paid for their donations. *Sydney Morning Herald*. 2019. <https://www.smh.com.au/lifestyle/health-and-wellness/life-saving-australian-heroes-should-be-paid-for-their-donations-20191010-p52zdd.html>. Accessed 2021 May 15.
64. Australian Red Cross LifeBlood. Donating plasma or platelets by apheresis. 2021; <https://www.donateblood.com.au/learn/apheresis>. Accessed 2021 May 15.
65. National Blood Authority Australia. Safety of blood products. 2021; <https://www.blood.gov.au/safety-blood-products>. Accessed 2021 May 15.
66. Australian Red Cross LifeBlood. Donate plasma. 2021; <https://www.donateblood.com.au/learn/plasma>. Accessed 2021 May 15.
67. Australian Red Cross LifeBlood. Variant Creutzfeldt-Jakob disease (vCJD) – I can't give blood as I lived in the UK for six months between 1980-1996. When will I be able to donate? [2021?]; <https://www.donateblood.com.au/faq/vcjd>. Accessed 2021 May 15.
68. New Zealand Blood Services. Give plasma. 2021; <https://www.nzblood.co.nz/give-plasma/>. Accessed 2021 May 16.
69. New Zealand Blood Services. Apheresis donor information. Auckland: New Zealand Blood Services; [date unknown]: <https://www.nzblood.co.nz/assets/Give-Blood/PDFs/111I008.pdf>. Accessed 2021 May 16.
70. New Zealand Blood Services. Annual Report 2019-20: saving lives - it's in our blood. Auckland: New Zealand Blood Services; 2020: https://www.nzblood.co.nz/assets/Uploads/19_WEB_NZBLOOD_2020_031220.pdf. Accessed 2021 May 16.
71. New Zealand Blood Services. Safe blood starts with you. Auckland: New Zealand Blood Services; 2020: <https://www.nzblood.co.nz/assets/Give-Blood/PDFs/111I080.pdf>. Accessed 2021 May 16.

New Zealand Blood Services. Eligibility criteria for new donors. 2021; <https://www.nzblood.co.nz/become-a-donor/am-i-eligible/new-donor-criteria/>. Accessed 2021 May 16.

73. NHS Blood and Transplant. Transition of the plasma programme: statement from Dr Gail Mifflin, Chief Medical Officer, NHS Blood and Transplant. 2021; <https://www.nhsbt.nhs.uk/news/transition-of-the-plasma-programme/>. Accessed 2021 May 12.
74. NHS Blood and Transplant. Give plasma. Bristol (UK): NHS Blood and Transplant; 2021: <https://nhsbt.dbe.blob.core.windows.net/umbraco-assets-corp/23382/2122-0059-pfm-leaflet-recruitment-v04.pdf>. Accessed 2021 May 12.
75. Sanquin. Bloeddonatie vergoeding. [2021?]; <https://www.sanquin.nl/bloed-doneren/vergoeding>. Accessed 2021 May 18. Dutch.
76. Sanquin. Bloedplasma doneren. 2021; <https://www.sanquin.nl/bloed-doneren/bloedplasma>. Accessed 2021 May 18. Dutch.
77. Etablissement français du sang [French Blood Establishment]. Les engagements de l'EFS. 2021; <https://www.efs.sante.fr/lefs-notre-action/les-engagements-de-lefs>. Accessed 2021 May 22. French.
78. Etablissement français du sang [French Blood Establishment]. Le don de plasma. [2021?]; <https://dondesang.efs.sante.fr/le-don-de-plasma>. Accessed 2021 May 22. French.
79. Rossi F. The organization of transfusion and fractionation in France and its regulation. *Annals of Blood*. 2018;3.
80. Etablissement français du sang [French Blood Establishment]. Tout savoir sur les contre-indications. [2021?]; <https://dondesang.efs.sante.fr/qui-peut-donner-les-contre-indications/tout-savoir-sur-les-contre-indications>. Accessed 2021 May 22. French.
81. Europlasma. Plasma donation procedure. 2021; <https://www.europlasma.at/en/donate-plasma/plasma-donation-process>. Accessed 2021 May 5.
82. Biolife. Homepage. 2021; <https://www.plasmazentrum.at/en/home-2/>. Accessed 2021 May 5.
83. Europlasma. Information for donors. 2021; <https://www.europlasma.at/en/donate-plasma/information-for-donors>. Accessed 2021 May 5.
84. UNICAPlasma. Novinky. 2021; <https://www.unicaplasma.cz/navysujeme-nahradu/>. Accessed 2021 May 5. Czech.
85. Sanaplasma. Výhody pro dárce. 2020; <https://www.sanaplasma.cz/vyhody-pro-darce>. Accessed 2021 May 5. Czech.
86. Cara Plasma. Výhody pro dárce. 2021; <https://www.caraplasma.cz/vyhody-pro-darce>. Accessed 2021 May 5. Czech.
87. UNICAPlasma. První návštěva. 2021; <https://www.unicaplasma.cz/prvni-navsteva/>. Accessed 2021 May 5. Czech.
88. Plasma Place. CO BYSTE MĚLI VĚDĚT O DAROVÁNÍ PLAZMY. [2021?]; <https://www.plasmaplace.cz/>. Accessed 2021 May 5. Czech.
89. Sanaplasma. Důležité informace pro dárce. 2020; <https://www.sanaplasma.cz/informace-o-odberu>. Accessed 2021 May 5. Czech.
90. Europlasma. 4 kroky: Jak probíhá odběr plazmy? 2021; <https://www.europlasma.cz/vse-o-odberu/jak-to-probiha.html>. Accessed 2021 May 5. Czech.
91. Octapharma Plasma. Erhalte ich Geld für meine Plasmaspende? 2021; <https://www.octapharmaplasma.de/aufwandsentschaedigung>. Accessed 2021 May 10. German.
92. Bundeszentrale für gesundheitliche Aufklärung (BZgA) [Federal Centre for Health Education Germany]. Ablauf einer Blut- und Plasmaspende. 2021; <https://www.blutspenden.de/blut-und-plasmaspende/ablauf-einer-blut-und-plasmaspende/>. Accessed 2021 May 10. German.
93. Bundeszentrale für gesundheitliche Aufklärung (BZgA) [Federal Centre for Health Education Germany]. Voraussetzungen für eine Blut- oder Plasmaspende. 2021; <https://www>

.blutspenden.de/blut-und-plasmaspende/voraussetzungen-fuer-eine-blut-oder-plasmaspende/.

Accessed 2021 May 10. German.

94. ImpactLife. Plasma apheresis. 2021; <https://www.bloodcenter.org/donate/donating-options/plasma/>. Accessed 2021 May 8.

95. Biolife. FAQs. 2020; <https://www.biolifeplasma.com/current-donor/faqs>. Accessed 2021 May 5.

96. CSL Plasma. Giving has its rewards: plasma donation rewards for current donors. 2021; <https://www.cslplasma.com/rewards-for-current-donors>. Accessed 2021 May 10.

97. Grifols. What is Grifols' donor compensation? 2019; <https://www.grifolsplasma.com/en/plasma-donor/how-to-donate/donation-fees>. Accessed 2021 May 5.

98. CSL Plasma. Plasma donation requirements & process. 2021; <https://www.cslplasma.com/become-a-donor>. Accessed 2021 May 10.

99. Grifols. Donation requirements. 2019; <https://www.grifolsplasma.com/en/plasma-donor/how-to-donate/donation-requirements>. Accessed 2021 May 5.

100. Biolife. Eligibility. 2020; <https://www.biolifeplasma.com/become-a-donor/eligibility>. Accessed 2021 May 5.

101. CSL Plasma. Your first donation. 2021; <https://www.cslplasma.com/become-a-donor/your-first-donation>. Accessed 2021 May 10.

102. National Blood Authority Australia. Annual Report 2019-20. Canberra: National Blood Authority Australia; 2020: <https://www.transparency.gov.au/annual-reports/national-blood-authority/reporting-year/2019-20>. Accessed 2021 May 25.

103. National Blood Authority Australia. Imported products. 2021; <https://www.blood.gov.au/imported-products>. Accessed 2021 May 15.

104. NHS Immunoglobulin Database. Annual Report 2019-20. Manchester (UK): MDSAS; 2021: <https://igd.mdsas.com/wp-content/uploads/ImmunoglobulinDatabaseAnnualReport201920.pdf> Accessed 2021 May 12.

105. Sanquin. Jaarverslag 2019. 2019; <https://www.sanquin.nl/binaries/content/assets/sanquinnl/over-sanquin/pers--actueel/jaarverslagen/sanquin-jaarverslag-2019.pdf>. Accessed 2021 May 18. Dutch.

106. Etablissement français du sang [French Blood Establishment]. Annual report 2019: the life of EFS in figures. Saint-Denis (France): EFS; 2020: https://www.efs.sante.fr/sites/instit/files/RA/EFS_Cahier_DATA_vFINAL_EN_WEB.pdf. Accessed 2021 May 22.

107. Prevot J, Jolles S. Global immunoglobulin supply: steaming towards the iceberg? *Curr Opin Allergy Clin Immunol*. 2020;20(6):557-564. [PMC free article: PMC7752222] [PubMed: 33044340]

108. Press J, Lindsay R. Business is booming for the \$24 billion plasma industry — but it may be putting vulnerable donors at risk. *Business Insider*. 2021 Mar 11. <https://www.businessinsider.com/plasma-donating-industry-vulnerable-health-2021-3>. Accessed 2021 May 5.

109. Stanworth SJ, New HV, Apolseth TO, et al. Effects of the COVID-19 pandemic on supply and use of blood for transfusion. *Lancet Haematol*. 2020;7(10):e756-e764. [PMC free article: PMC7333996] [PubMed: 32628911]

110. Whitmore M. Plasma donation and IG supply: an interview with IDF President and CEO John Boyle. *IG Living*. 2021(Feb-Mar). https://www.igliving.com/magazine/articles/IGL_2021-02_AR_Plasma-Donation-and-IG-Supply.pdf. Accessed 2021 May 12.

111. New Zealand Blood Service. Statement of Intent: 1 July 2020 - 30 June 2024. Auckland (NZ): New Zealand Blood Service; 2020: <https://www.nzblood.co.nz/assets/Uploads/NZBS-Statement-of-Intent-2020-2024.pdf>. Accessed 2021 May 22.

112. McNeil M. Plasma donations drop during pandemic, donation centers play catch-up. *KOLD News* 13. 2021 May 26. <https://www.kold.com/2021/05/27/plasma-donations-drop-during-pandemic-donation-centers-play-catch-up/>. Accessed 2021 Aug 4.
113. Sanquin. Annual Report 2018. Amsterdam: Sanguin; 2019: https://www.sanquin.nl/binaries/content/assets/sanquinen/about-sanquin/annual-reports/sanquin_annual_report_2018.pdf. Accessed 2021 May 18.
114. Sanquin. De bloedtest bij Sanquin. 2021; <https://www.sanquin.nl/bloed-doneren/mag-ik-bloed-geven/bloedtest>. Accessed 2021 May 18. Dutch.
115. New Zealand Blood Services. CJD Creutzfeldt-Jakob disease: Information for blood donors. Auckland: New Zealand Blood Services; 2019: <https://www.nzblood.co.nz/assets/Give-Blood/PDFs/111I077.pdf>. Accessed 2021 May 16.
116. EU Directive 2002/98/EC of the European Council. *Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC*. 2002; <https://www.legislation.gov.uk/eudr/2002/98/body>. Accessed 2021 Jun 2.
117. Committee for Proprietary Medicinal Products (CPMP). Guidelines on requirements for plasma master file (PMF) certification. 2004: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-plasma-master-file-pmf-certification_en.pdf. Accessed 2021 Jun 2.
118. WHO. Blood products and related biologicals: good manufacturing practices. [2019?]; <https://www.who.int/bloodproducts/gmp/en/>. Accessed 2021 Jun 2.
119. Title 21: Food and Drugs. Electronic Code of Federal Regulations (e-CFR); 2021: https://www.ecfr.gov/cgi-bin/text-idx?SID=3ee286332416f26a91d9e6d786a604ab&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl Accessed 2021 Jun 2.
120. Guidelines for the Blood Transfusion Services in the United Kingdom, 7th edition. London: TSO (The Stationery Office); 2005: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/228828/0117033715.pdf. Accessed 2021 Jun 2.
121. National Blood Authority Australia. What blood products are supplied - National Product Price List. 2021 Jul 1; <https://www.blood.gov.au/national-product-price-list>. Accessed 2021 May 15.
122. Crampton E. It's time to think seriously about paying blood donors. *Stuff Business*. 2020. <https://www.stuff.co.nz/business/300034339/its-time-to-think-seriously-about-paying-blood-donors> Accessed 2021 May 15.
123. CSL Behring. Our company. 2021; <https://www.cslbehring.com.au/our-company>. Accessed 2021 May 15.
124. LFB Biomedicaments S.A. Nos médicaments. 2017; <https://lesmedicamentslfb.lfb-agera.com/fr/page/nos-medicaments>. Accessed 2021 May 22. French.
125. Liste des médicaments commercialisés par LFB BIOMEDICAMENTS, en France. Courtaboeuf Cedex (France): LFB Biomedicaments S.A.; 2021: <https://www.groupe-lfb.com/lfb-content/uploads/2021/03/liste-des-medicaments-commercialises-par-lfb-2020.pdf>. Accessed 2021 May 22. French.
126. LFB. Process for buy out of Austrian Plasma Collection Group [news release]. Les Ulis (France): LFB; 2010 Jun 22: <https://www.groupe-lfb.com/en/news/process-for-buy-out-of-austrian-plasma-collection-group/>. Accessed 2021 May 5.
127. New Zealand Blood Services. What is blood used for? 2021; <https://www.nzblood.co.nz/about-blood/what-blood-is-used-for/>. Accessed 2021 May 16.
- 128.

MedSafe. Medicines data sheets. 2021; [https://www.medsafe.govt](https://www.medsafe.govt.nz/profs/datasheet/datasheet.htm)

[.nz/profs/datasheet/datasheet.htm](https://www.medsafe.govt.nz/profs/datasheet/datasheet.htm). Accessed 2021 May 16.

129. Sinclair J. Intravenous immunoglobulin (IVIG) therapy. In: Williams G, ed. *Starship child health clinical guideline*. Auckland (New Zealand): Starship Children's Health; 2020: <https://www.starship.org.nz/guidelines/intravenous-immunoglobulin-ivig-therapy/>. Accessed 2021 May 16.
130. Sanquin. Mag ik plasma geven? 2021; <https://www.sanquin.nl/bloed-doneren/mag-ik-plasma-geven>. Accessed 2021 May 18. Dutch.
131. Sanquin. Fijn dat je weer plasma komt geven! 2021; <https://www.sanquin.nl/donortest/plasma>. Accessed 2021 May 18. Dutch.
132. Sanquin Plasma Products. Kritische zorg. 2021; <https://www.plasmaproducts.com/nl/voor-professionals/productoverzicht/kritische-zorg/index>. Accessed 2021 May 18. Dutch.
133. Sanquin Plasma Products. Stollingsstoornissen: Van Factor VIII & IX tot Protrombine Complex. 2021; <https://www.plasmaproducts.com/nl/voor-professionals/productoverzicht/stollingsstoornissen/index>. Accessed 2021 May 18. Dutch.
134. Sanquin Plasma Products. Immunoglobulinen. 2021; <https://www.plasmaproducts.com/nl/voor-professionals/productoverzicht/immunoglobulinen/index>. Accessed 2021 May 18. Dutch.
135. NHS Scotland. Plasma products. 2020; <https://www.nss.nhs.scot/blood-tissues-and-cells/blood-components/plasma-products/>. Accessed 2021 May 12.
136. Bio Products Laboratory Ltd. About BPL Group. 2021; <http://www.bplgroup.com/about-bpl-group/>. Accessed 2021 May 12.
137. Grifols. Buddy Bonus Program. 2019; <https://www.grifolsplasma.com/en/returning-plasma-donors/buddy-bonus-program>. Accessed 2021 May 5.

Appendix 1. Country Profiles

Note that this appendix has not been copy-edited.

Australia

Plasma Collectors and Plasma Fractionators

The National Blood Authority (NBA) is the statutory authority that manages and coordinates the supply of blood, blood products and blood services and their use, on behalf of the Australian Government and state and territory governments.^{11,12} Under a contract with the NBA, the Australian Red Cross Lifeblood (Lifeblood) (formerly the Australian Red Cross Blood Service) is responsible for all blood collections, including plasma (source and recovered).^{13,14}

Most PDMPs distributed in Australia are manufactured by CSL Behring from plasma collected by the Australian Red Cross Lifeblood under the National Fractionation Agreement for Australia (NaFAA). This toll manufacturing agreement was established on January 1, 2018 and continues until December 31, 2026 and assures the “provision of a safe, secure and affordable supply of plasma products to the Australian community.”⁵³ Plasma products are imported into Australia only when domestic supply cannot meet need, or where there are supply chain issues.⁵³

Donor Status, Requirements, and Frequency

Blood or plasma donors in Australia do not receive any material compensation – money or otherwise.^{62,63}

Donors must be between 18 and 75 years old, healthy and weigh more than 50 kg.⁶⁶ Plasma donation is permitted every 2 weeks.⁶⁴

Donors are screened based on an interview, a mini-physical check, health assessment, declaration about high-risk behaviour, practices and circumstances that prevents them from donating blood, among others. The eligibility criteria are outlined in the Guidelines for the Selection of Blood Donors (GSBD). Each unit of the donated blood is tested for HIV, HCV, HBV, HTLV 1/2; and syphilis. As a safety precaution, all donations can be tracked from entry point in the system to the final product and recipient.^{62,65}

Due to risk of Creutzfeldt-Jakob Disease (CJD) transmission in Australia, Lifeblood does not allow donations from people who lived in the UK for 6 months or more from 1980 to 1996.⁶⁷

Consumption and Self-Sufficiency

Almost half of all blood donations in Australia are plasma donations.⁶⁶ In 2019 to 20, Lifeblood collected 803 tons of plasma; and CSL Behring produced 3,282.7 kg of domestic Ig.¹⁰²

The NBA also procures blood products from overseas when such products are not manufactured in Australia or the Australian system is unable to produce enough product to meet demand.¹³ For example, NBA imports IV immunoglobulins (IVIg), as domestic production does not meet demand. NBA also imports PDMPs that are largely used for the treatment of hemophilia, as these products are not produced in Australia.¹⁰³

The rate of growth of Ig consumption has declined over the years to approximately 6.7% in 2019 to 20 compared to 7.2% in 2018 to 19 and 10.6% in 2017 to 18. In 2019 to 20 a total of 7.01 million grams of Ig was used nationally, representing a total cost (including the cost of plasma collections) of \$637.1 million. Of the 7.01 million grams, 46% of Ig was produced in Australia and 54% was imported.¹⁰²

Domestic Versus Imported Plasma Products

As of July 2020, CSL Behring supplied the following PDMPs from the plasma collected by Lifeblood: Albumin, Factor VIII, Factor IX, Human Prothrombin complex, Antithrombin III concentrate, IV immunoglobulin (IVIg), Subcutaneous immunoglobulin (SCIg), Normal immunoglobulin (NIg), CMV immunoglobulin, Hepatitis B immunoglobulin, Rho(D) Ig (Glycine Formulation), Tetanus immunoglobulin and Zoster immunoglobulin.^{14,121}

As of July 2020, CSL Behring, Grifols, Octapharma and Takeda imported IVIg, SCIg and Rho(D)Ig to Australia. CSL Behring and Takeda Pharmaceuticals Australia also supplied imported Factor VIII, Activated Prothrombin Complex Concentrate (APCC), Factor XI, Factor XIII, Fibrinogen, Protein C, and C1 Esterase Inhibitor.^{14,121} These plasma products were primarily derived from compensated US and European donors.^{1,63,122,123}

Austria

Plasma Collectors and Plasma Fractionators

In addition to public or not-for-profit institutions, Austria also permits private plasmapheresis centres to collect source plasma for fractionation. Specifically, the private plasmapheresis centres collect most of the source plasma for fractionation and manufacturing PDMPs.³

Austrian Red Cross is the non-profit organization that collects whole blood, which is tested, separated into various blood components, and processed into different blood products and then given to patients.²⁸

Private plasmapheresis centres operating in Austria include BioLife Plasmazentrum, Europlasma Spendezentrum and Plasmavita Plasma Center. Collectively, they have more than 15 source plasma collection centres in Austria.^{29,30}

Of note, biopharmaceuticals like Takeda and Octapharma have PDMP manufacturing plants in Austria.⁴⁸

Donor Status, Requirements, and Frequency

While whole blood donors are non-renumerated at non-for-profit institutions, donors at plasmapheresis centres are paid for plasma used toward fractionation. Monetary compensation is provided for time and inconvenience related to donation with a fixed sum of money irrespective of actual costs established by blood establishments. Donors are compensated per donation, which is usually 25 euros. Some plasma collection centres also give incentives for first-time donation (e.g., 50 euros) and for loyal donors (e.g., extra 75 euros for every 10th donation).^{81,82} Other incentives include food vouchers, small tokens, and time off work (public sector, 1 day).⁵⁷

Eligible individuals can donate plasma up to 50 times in a reference year in Austria; once within 72 hours, twice in 7 days, and 3 times in 14 days. A maximum donation of 700 mL plasma per visit is allowed.^{3,81} Donors must be between 18 and 60 years old, healthy and weigh between 50 kg to 150 kg, with a BMI below 40. Plasma donation from donors who are 60 to 64 years old is possible provided they have donated before and have approval from the physician.⁸³

Donors are generally screened through an interview and medical exams; and required to present valid identification (e.g., passport, driving licence). For example, Europlasma requires first-time donors or those who have donated before 6 months, to go through a health check. The health check includes vital signs, a thorough medical examination, a detailed anamnesis interview, and blood/laboratory tests. Donors will have to wait for a week for the blood test results to be available; and if eligible, can donate plasma after the 1-week waiting period. The medical examination is repeated every 4 weeks. Blood pressure, pulse, weight and body temperature are measured before every donation and blood findings such as hemoglobin levels are measured during the donation. The collected blood plasma is tested after each donation for HBV, HCV, HIV and total protein.⁸¹

Self-Sufficiency and Consumption

In 2017, 655,000 litres of plasma (source and recovered) for fractionation was collected in Austria.³ In 2014, it was suggested that Austria's self-sufficiency ratio for Ig therapy was 100%.⁵ In 2014, Austria collected 56.6 litres per 1,000 people which increased 75 litres per 1,000 people in 2017.^{1,5}

Czech Republic

Plasma Collectors and Plasma Fractionators

In addition to public or not-for-profit institutions, the Czech Republic also permits private plasmapheresis centres to collect source plasma for fractionation. The private plasmapheresis centres collect most of the source plasma for fractionation and manufacturing of PDMPs.³¹

Not-for-profit institutions that collect whole blood fall under the regional or university hospitals as their specialized departments.³¹

Private plasmapheresis centres operating in the Czech Republic include Caraplasma, Europlasma, Plasma Place, Sanaplasma and UNICAplasma. Collectively they have more than 25 source plasma collection centres in the Czech Republic.^{30,32-36}

Donor Status, Requirements, and Frequency

While whole blood donors are non-renumerated at non-for-profit institution, donors at plasmapheresis centres are paid for plasma used toward fractionation. Compensation is linked to loss of earnings, and for inconvenience related to donating. A fixed sum of money is provided irrespective of actual costs established by the blood establishment. Donors are compensated per donation which is usually 700 CZK (approximately C\$40). To encourage a second donation, some collection centres give 400 CZK of the 700 CZK at the time of the first donation; and 1000 CZK at the time of the second donation. Of note, if a donor provides only 1 donation, the donated plasma cannot be used to make PDMPs and must be discarded. In place of the 700 CZK, donors can opt for a tax rebate and 1 day of paid leave from work. Some plasma collection centres also give incentives for referring a donor (e.g., 500 CZK) and give in-kind gifts for loyal donors at regular intervals.^{34,84-86} Other incentives include food vouchers, small tokens, reimbursement of costs linked to travel and time off work in both the public and private sector.⁵⁷

Eligible individuals can donate plasma once every 14 days. Donors must be between 18 and 65 years old, healthy and weigh more than 50 kg.⁸⁸ Depending on the weight, a donation of 650mL to 850 mL plasma per visit is allowed, with a maximum of 25 litres per year. However, a maximum of 1.5 litres of plasma can be donated per week if IV fluid replacement is given.^{3,87} While donors do not have to be Czech citizens, they must have proof of long-term residence, a permanent address, and a valid health insurance.⁸⁸

Donors are generally screened through an interview and medical exams; and are required to present valid identification and proof of health insurance. If the laboratory results are acceptable, some plasma collection centres (e.g., Caraplasma, Sanaplasma and UNICAplasma) allow donation on the same visit, and there are no wait periods.^{36,87,89} However, Europlasma does not allow donation on the same day. There is a 7 day wait period until the results of the laboratory test are available. The collected blood plasma is tested after each donation for HAV, HBV, HCV, HIV, syphilis, and parvovirus B19.⁹⁰

Self-Sufficiency and Consumption

Since the private plasmapheresis centres were permitted to operate and provide monetary compensation to plasma donors in 2007, the per capita donations increased. Plasma donation increased from around 5 litres per 1,000 people in 2007 to around 33 litres per 1,000 people in 2014. In 2017, there were 481,000 litres of plasma (source and recovered) for fractionation collected in the Czech Republic, representing 45 litres per 1,000 people.³ In 2014, it was suggested that the Czech Republic's self-sufficiency ratio for Ig therapy was 100%.⁵

France

Plasma Collectors and Plasma Fractionators

The French Blood Establishment (EFS) is a public organization responsible for the collection, testing, preparation, and distribution of all blood products, including plasma.^{25,26}

Laboratoire Français du Fractionnement et des Biotechnologies (LFB) holds the exclusive right for plasma fractionation resulting from blood donations collected by the EFS.⁵⁰ The LFB Group, a French biopharmaceutical company, is a limited company with the French state as the sole shareholder.²⁷ EFS supplies the collected plasma to the LFB for fractionation to manufacture PDMPs.^{25,26} LFB sells the PDMP derived from French plasma on the domestic market. French hospitals, however, are free to purchase any brands of plasma-derived medicinal products registered for sale in France, and do not necessarily have to purchase LFB products.⁵¹

France is the only country that restricts the import of PDMPs from plasma acquired through paid donors.⁴⁹ Only in the case of shortages does the French government seek support from foreign companies in the production of PDMPs from plasma acquired from volunteer non-renumerated donors.⁵¹ In addition to fractionating plasma collection within France, the LFB undertakes contract fractionation for other not-for-profit entities in Belgium, Luxembourg, Brazil and Morocco and also sells finished plasma products on the international markets.⁵¹ France has an open domestic market for PDMPs which allows hospitals in France to purchase their own PDMPs registered for sale in that country from any desired commercial manufacturer.⁵¹

Of note, biopharmaceutical LFB and Octapharma have PDMP manufacturing plants in France.⁴⁸

Donor Status, Requirements, and Frequency

Blood or plasma donors in France do not receive any material compensation – money or otherwise.⁷⁷

Plasma can be donated 24 times a year; with a minimum of 2-week gap between a plasma donation and any other donation.⁷⁸ A maximum donation of 750 mL plasma per visit is allowed.³ Donors must be between 18 and 66 years old and weigh more than 55 kg.⁷⁸

Donors are screened based on questionnaire, an interview, physical check-up (at the time of first donation) and mandatory tests for viral and bacterial infections.⁷⁸ Plasma is tested for HIV, HBV, HCV, and HTLV. Additionally, as a safety precaution, all donations can be tracked from entry point in the system to the final product and recipient.⁷⁹

Due to risk of CJD transmission, people who resided in the UK between 1980 and 1996 for a cumulative period of 1 year are not allowed to donate.⁸⁰

Self-Sufficiency and Consumption

In 2019, EFS issued 897,735 litres of plasma to LFB, representing a 0.9% increase compared to 2018. These donations were collected from fixed sites as well as through mobile collections.¹⁰⁶ LFB, which has exclusive access to EFS donated plasma collected on French territory, gives priority to national needs, treating more than 500,000 patients each year in France with a portfolio of 23 PDMPs.⁷⁹ However, Garraud 2019 highlights that LFB manufactured drugs compete with other brands in an open market; and the French hospitals' use of PDMPs from paid donors has reached close to 50%.⁵² In 2014, France's self-sufficiency ratio for Ig was 54%.⁵ In 2017, France consumed 10,873 kg of Ig (approximately 2,718,000 litres of plasma) against the 892,000 litres of plasma collected, representing a shortfall of 1,826,000 litres.¹

Domestic Versus Imported Plasma Products

LFB manufactures the following PDMPs: antithrombin, alpha-1 antitrypsin, Factor IX, Factor VIII, Factor XI, fibrinogen, prothrombin complex, IVIg, Nig, Hepatitis B immunoglobulin, Zoster immunoglobulin and Tetanus immunoglobulin, albumin, von Willebrand factor and von Willebrand factor and factor VIII.^{124,125} Of note, LFB also manufactures PDMPs for the international market, albeit the PDMPs available for export are not manufactured from the plasma collected from donors in France.¹²⁶

Germany

Plasma Collectors and Plasma Fractionators

In addition to public or not-for-profit institutions, Germany also permits private plasmapheresis centres to collect source plasma for fractionation. The public or non-profit sector includes the German Red Cross, and hospital blood banks. The private sector includes the plasma processing industry and private plasmapheresis centres. The private plasmapheresis centres collect most of the source plasma for fractionation and manufacturing of PDMPs.³⁷⁻³⁹

Some German Red Cross centres also offer opportunity for plasmapheresis.⁴⁰ Information on if or how the German Red Cross processes the collected plasma for fractionation, was not available.

Private plasmapheresis centres operating in Germany include Blut-und Plamsaspendezentrum, CSL Plasma, Haema Blutspendezentrum, Octapharma GmbH, Plasma Services Europe, Plasmaspende, Plasmavita Plasma Center and Ruhr Plasma Center. Collectively they have more than 85 plasma collection sites in Germany.³⁰

Of note, biopharmaceuticals like Biotest, CSL Behring and Octapharma have PDMP manufacturing plants in Germany.⁴⁸

Donor Status, Requirements, and Frequency

While whole blood donors are non-renumerated at non-for-profit institution, donors at plasmapheresis centres are paid for plasma used toward fractionation. The framework for compensation is outlined in Section 10 of the German Transfusion Act, which is based on the direct effort of the respective type of donation.⁹¹ This compensation can be up to 25 euros or gifts.^{1,92} Other incentives include small tokens, free physical check-up (beyond what is required for donation), free or reimbursement for medical costs (e.g., additional medications), and time of work (public and private sectors).⁵⁷

Eligible individuals can donate plasma 60 times a year, with at least a 2 to 3 days gap between 2 plasma donations; and between a plasma and blood donation. Donors must be between 18 and 68 years old (with first donation by 60 years of age), healthy and weigh more than 50 kg. Donors must have donated blood at least once before the plasma donation to make the plasma donation immediately.^{40,93} Depending on the weight, a maximum donation of 650 mL to 850 mL plasma (including anticoagulant) per visit is allowed (650 mL for ≤ 60 kg, 750 mL for ≤ 80 kg, and 850 mL for > 80 kg).^{3,40} Donors must present an official photo identification and a blood donation card, which 1 receives after their first blood donation.⁹²

Donors are screened through a questionnaire, a blood test to determine hemoglobin level, and a health check.⁹²

Self-Sufficiency and Consumption

In 2017, 2,980,000 litres of both source and recovered plasma for fractionation were collected in Germany. In 2017, the private plasmapheresis centres collected 1.9 million litres which represented 63.8% of source plasma for fractionation. The remaining plasma for fractionation was collected through whole blood donation by German Red Cross (850,000 litres) and State-run, non-profit limited liability donation services, donation services at municipal or private hospitals, and the German Army (230,000 litres).^{37,39}

In 2014, it was reported that Germany's self-sufficiency ratio for Ig therapy was 100%.⁵ In 2014, Germany collected 31.6 litres per 1,000 people which increased to 36 litres per 1,000 people in 2017.^{1,5} In 2017, Germany consumed 2,258,000 litres of plasma, against a collection of 2,962,000 litres, representing a surplus of 704,000 litres.¹ Of note, some plasma products are imported as not all PDMPS are exclusively manufactured in Germany.³⁷

New Zealand

Plasma Collectors and Plasma Fractionators

New Zealand Blood Service (NZBS) is a not-for-profit Crown entity responsible for the collection, processing, testing and storage as well as distribution of all blood and blood products, including plasma in New Zealand.¹⁵

New Zealand has a toll manufacturing agreement with CSL Behring in Australia which imposes that plasma collected in NZBS is fractionated into PDMPs and returned to New Zealand for distribution and use.⁵⁴ The manufacturing contract with the fractionator includes plasma specifications and incorporates an agreement to sell surplus plasma-derived factor VIII and albumin back to the fractionator. The current toll fractionation agreement is valid until June 30, 2022.⁵¹

Donor Status, Requirements, and Frequency

Blood or plasma donors in New Zealand do not receive any material compensation — money or otherwise.⁶⁸

Donors must be between 18 and 60 years old, healthy and weigh more than 50 kg.⁷² Plasma can be donated every 2 weeks. Upon completing a whole blood donation, there is a 4-week wait time for donating plasma.⁶⁸

Donors are screened based on an interview, a physical check-up (at the time of first donation) and mandatory tests performed in accordance with the NZBS Manufacturing Standards (as approved by Medsafe), including testing for HIV, HBV, HCV, HTLV and syphilis. Other blood tests are also performed occasionally to ensure that the levels of proteins and blood counts remain normal in the donor's blood.⁶⁹⁻⁷¹

Due to risk of CJD transmission, NZBS does not allow blood or plasma donation for people who have visited or lived in the UK, France or the Republic of Ireland between January 1, 1980 to December 31, 1996 for a total period of 6 months or longer; or have received a blood transfusion in the UK, France, or the Republic of Ireland since 1980.¹¹⁵

Self-Sufficiency and Consumption

About 77,936 units of plasma were collected in New Zealand in 2019 to 20 across 9 fixed donor centres. New Zealand also piloted mobile plasma drives in 2019, which demonstrated that portable plasma collection is not only feasible but desirable.⁷⁰

Plasma from New Zealand donors met 88% of Ig (IVIg and SCIg) demand in 2019 to 20. The remaining 12% was supplemented using commercially supplied imported products. While 45% of the plasma required to manufacture IVIg was derived from recovered plasma (donations collected to meet the supply of red cell and platelet blood components), the remaining 55% was obtained from source plasma (plasmapheresis donations). Prior to mid-2019, demand for Ig increased at the rate of 8% annually. However, since mid-2019 the demand for Ig has increased significantly to 13 to 15% per annum. Total immunoglobulin product issued per 1,000 people was 96 g in 2019 to 20.⁷⁰

Domestic Versus Imported Plasma Products

NZBS contracts CSL Behring to manufacture PDMPs based on volunteer (non-remunerated) plasma donated in New Zealand as well as imported plasma from overseas. A small number of PDMPs and recombinant blood products manufactured overseas are sourced from other New Zealand distributors.¹⁶

CSL Behring supplies the following PDMPs from the plasma collected by NZBS: Albumin, Factor VIII, Rho(D)Ig, Factor II, IX and X concentrate, antithrombin III, IVIg, SCIg, and NIg, Hepatitis B immunoglobulin, Zoster immunoglobulin and Tetanus immunoglobulin.^{70,127,128}

CSL Behring also manufactures PDMPs from the plasma collected overseas. For example, Privigen, an IVIg, is prepared from pooled plasma donations from compensated European and US donors.¹²⁹

The Netherlands

Plasma Collectors and Plasma Fractionators

Based on the Blood Supply Act, Sanquin is the only blood establishment in the Netherlands authorized to manage the supply of blood and blood products. Sanquin, a not-for-profit organization was established in 1998 through a merger between the Dutch blood banks and the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (CLB).²⁴

Plasma collected by Sanquin is processed by Sanquin Plasma Products (SPP) which is located in the Netherlands and buys plasma from Sanquin blood banks for the production of PDMPs primarily for domestic consumption.^{48,51} On behalf of Sanquin, SPP provides the Dutch health service with PDMPs from plasma collected in the Netherlands.¹⁹ If Sanquin has a surplus of plasma intermediaries or finished products over the domestic demand, such excess may be sold to another not-for-profit entity or, if this is not possible, on the open international market.⁵¹ All importation activity is restricted to Sanquin.

Of note, Netherlands has an open domestic market in respect of PDMPs which allows hospitals to purchase their own PDMPs registered for sale in that country from any desired commercial manufacturer.⁵¹

Donor Status, Requirements, and Frequency

Blood or plasma donors in the Netherlands do not receive any material compensation — money or otherwise. However, Sanquin offers incentives such as in-kind gifts, small tokens, free or reimbursement of medical costs (e.g., additional medications), reimbursement of cost linked to travel (to and from donation) and time off work.^{57,75}

Plasma can be donated every 2 weeks up to a maximum of 26 times a year. Plasma donors are not allowed to donate whole blood.⁷⁶ A maximum donation of 650 mL plasma per visit is allowed.³ Donors must be between 18 and 65 years old, healthy and weigh more than 55 kg.¹³⁰

Donors are screened by a medical questionnaire and a medical examination.¹³¹ Each donation is tested for HIV, HBV, HCV, HEV and syphilis. First-time donors are also tested for HTLV-1/2.^{113,114}

Self-Sufficiency and Consumption

In 2017, the Netherlands' plasma collection rate was 19 litres per 1,000 people.¹ In 2019, Sanquin supplied approximately 320,000 kg of plasma (including apheresis) delivered to SPP.¹⁰⁵ Due to the increasing demand of Ig, SPP has an agreement in place with a cooperation partner in Hungary. In 2019, SPP received 60,000 kg of plasma from Hungarian donors. With an agreement in place for 2 new collection centres in Hungary, this number was expected to increase to 100,000 kg in 2020.¹⁰⁵

Domestic Versus Imported Plasma Products

SPP domestic production includes IVIg, Rho(D)Ig, hepatitis B immunoglobulin, Zoster immunoglobulin and Tetanus immunoglobulin, Prothrombin Complex (containing Factors II, VII, IX and X), factor VIII, von Willebrand factor and albumin.¹³²⁻¹³⁴

United Kingdom

Plasma Collectors and Plasma Fractionators

In the UK, the following blood services organizations exist: NHS Blood and Transplant (NHSBT) for England, the Scottish National Blood Transfusion Service (SNBTS), the Welsh Blood Service (WBS) and the Northern Ireland Blood Transfusion Service (NIBTS).¹⁷

Since 1998, the UK had restriction on using plasma from UK donors for the fractionation to make PDMPs. The restriction was in place due to risk of CJD transmission. This restriction was lifted in February 2021, after the independent Commission on Human Medicines (CHM) advised that plasma collection in UK is safe and can resume supported by a set of safety measures. The safety measures refer to all relevant risk-mitigation measures already established for blood components for transfusion (the use of leucodepletion, deferral of high-risk donors and traceability between donor and recipient). Manufacturers must apply to the Medicines and Health care products Regulatory Agency (MHRA) to vary the terms of their existing licenses to introduce the use of UK-sourced plasma as well as product-specific risk assessment and an evaluation of the prion reduction capacity of the product manufacturing process. Each product will need to be individually reviewed and evaluated by the MHRA, and advice sought from the CHM's Clinical Trials, Biologicals and Vaccines Expert Advisory Group and CHM.¹⁸ The announcement also highlighted efforts to introduce a new condition to ensure that UK plasma is used first by UK patients and not exported to meet contracts elsewhere. No further information on this condition was available.⁵⁵

Starting in April 2021, the NHSBT started taking plasma donations for fractionation across 14 plasma collection centres around England, for an initial period of 3 months.^{20,21} The plasma collected will be stored and supplied to 1 or more fractionators appointed by NHS England, later in the year 2021.²⁰ Similarly, the SNBTS has also started plasma collection since the restriction was lifted.^{22,23} It is unknown if the WBS and the NIBTS have started plasma collection for fractionation.

NHS England is responsible for the supply of Ig therapy in England and Northern Ireland through the Commercial Medicines Unit (CMU). NHS Wales and NHS Scotland have separate agreements for Ig therapy which are managed directly by each nation's procurement teams.^{104,135}

Of note, biopharmaceutical Bio Products Laboratory (BPL) have PDMP manufacturing plants in the UK.⁴⁸

Donor Status, Requirements, and Frequency

Blood or plasma donors in the UK do not receive any material compensation – money or otherwise.^{21,73}

Donors must be between 18 and 66 years old to donate.⁷⁴ Additional information on donor requirements and frequency of plasma donation was not available in the literature.

Self-Sufficiency and Consumption

The UK, up until now, was entirely dependent on imported blood plasma from other countries, primarily the US.²⁰

According to the NHS immunoglobulin database, NHS England purchased 6,194,613 g of plasma in 2016 to 17 (8% annual increase), 6,745,697 g in 2017 to 18 (9% annual growth) and 7,575,127 g in 2018 to 19 (12% annual growth) followed by 5,783,782 g in 2019 to 20 (14% annual decline). An increased order of Ig toward the end of 2018 to 19, as well as an overall decline in therapy due to the COVID-19 pandemic may be some of the reasons for the annual decline in 2019 to 20. Despite the volume reduction, the total expenditure on Ig cost increased from £229 million in 2018 to 19 to £245million in 2019 to 20. This was attributed to the increase in product cost.¹⁰⁴

Domestic Versus Imported Plasma Products

The UK, up until February 2021, was entirely dependent on imported blood plasma to make plasma products.²⁰

The UK government created a company called Plasma Resources UK (PRUK) in response to the decision in 1998 to stop using UK plasma for fractionation. PRUK imported plasma from the US and manufactured fractionated plasma medicines for NHS patients. PRUK had a branch in the US and the BPL in England. BPL was a state-owned organization as a part of the NHS Blood. In 2013, 80% of BPL shares was sold to a private company, with the PRUK holding 20%. Since 2016, BPL has been privately owned, and BPL Therapeutics (part of BPL) supplies PDMPs to the NHS in the UK as well as to international markets.^{21,136}

In addition to BPL, other suppliers of PDMPs in the UK were Biotest (UK) Ltd., CSL Behring UK Ltd., Grifols UK, LFB, Octapharma, and Takeda in 2019 to 20.¹⁰⁴

United States

Plasma Collectors and Plasma Fractionators

In addition to public or not-for-profit institutions, the US also permits private plasmapheresis centres to collect source plasma for fractionation.⁴² The majority of the plasma for fractionation is collected by the private plasmapheresis centres.⁴¹

The American Red Cross, a non-profit organization, collects plasma from individuals with AB blood type only. This plasma is used for burn and trauma patients.⁴² There are also independent non-profit community-based blood centres in US which collect blood and blood components.⁴³

Private plasmapheresis centres operating in the US include Access Plasma LLC, ADMA BioCenters, B Positive Plasma LLC, BioLife Plasma Services LP, Biomat US LLC, Blood and Plasma Research Inc., BPL Plasma Inc., CSL Plasma, GCAM Plasma Inc., Grifols Biomat US, Grifols Talecris Plasma Resource Inc., Hemarus LLC, Immunotek Bio Centers LLC., KEDPLASMA LLC, Octapharma Plasma Inc., Prometic Plasma Resources, Saturn Biomedical, Scantibodies Biologics, Inc. and Southern Blood Services. Collectively they have more than 900 plasma collection sites in the US.³⁰ Of note, the US FDA restricts the use of source plasma to non-transfusable purposes only, that is, for fractionation and manufacturing of PDMPs.⁷

FDA laws permit the importation of plasma provided they comply with section 351(a) of the Public Health Services Act, or if FDA permits such imports “under appropriate circumstances and conditions” as determined by the Center for Biologics Evaluation and Research.⁵⁶ Provisions relating to the security of domestic plasma, fractionation and PDMP supply were unavailable in the literature.

Biopharmaceuticals like Grifols, Takeda, ADMA Biologics, CSL Behring, Kedrion US and Emergent BioSolutions have PDMP manufacturing plants in the US.⁴⁸

Donor Status, Requirements, and Frequency

The American Red Cross or the independent community-based blood centres do not compensate donors for plasma donation. The American Red Cross permits plasma donation from the AB blood group only. This plasma is used in emergency and trauma situations to help stop bleeding.⁴² Eligible donors can donate every 28 days up to 13 times a year.^{42,43,94} Plasma donation can be made 8 weeks after a whole blood donation; and 16 weeks after a donation of double unit of red blood cells.⁹⁵

Private plasmapheresis centres compensate plasma donors. Cash compensation usually ranges from US\$35 to US\$65 per donation in prepaid debit cards.^{108,137} In 2019, plasma companies paid about US\$2.7 billion to US plasma donors, which was an average of US\$50 per donation.¹⁰⁸ In addition, there are referral bonuses (e.g., US\$100 if the referral makes 2 donations), rewards programs, and incentives for those who donate twice a week or 8 times a month.^{108,137} For example, new donors can make up to US\$1,000 in their first month.^{96,97} The usual rate may vary by location, but donors can make an average of US\$400 a month through plasma donation.⁹⁷

As per the US FDA regulations, plasma donors can donate once in a 2-day period however no more than twice in a 7-day period.^{7,41} The minimum age of a donor is 18 years and the maximum age can vary between 65 to 69 years. Donors must be healthy and weigh more than 50 kg.⁹⁸⁻¹⁰⁰

Depending on the weight, a maximum donation of 625 mL to 800 mL plasma per visit is allowed (625 mL for 100 to 149 lbs; 750 mL for 150 to 174 lbs; and 800 mL for > 175 lbs).³ Donors must have a valid government-issued photo identification, proof of social security number, and proof of

local residency. Those without a social security number must provide a PRC, BCC or Laser Visa Number. Residents of Mexico can also donate and have to provide a valid BCC or US Visa and Government-issued document indicating the Clave Única de Registro de Población number.⁹⁹⁻¹⁰¹

Donors are generally screened through an interview and a general health screening is performed at each donation. Health screening includes a test of the blood sample for anemia and protein level, and a check of vital signs. First-time donors also go through a physical exam, which is repeated every year.^{7,99-101} Regulations require source plasma to be tested for HIV, HCV, HBV and syphilis at the first donation and every 4 months. Recovered plasma is tested for HIV, HCV, HBV, syphilis, HTLV 1/2, West Nile virus, Chagas disease at every donation.⁷

Self-Sufficiency and Consumption

In 2017, US consumed 46% of Ig sold worldwide. However, the same year it supplied 65% of the plasma used worldwide, making it the largest supplier of plasma for fractionation in the world.^{41,107} In 2014, it was reported that that US’s self-sufficiency ratio for Ig therapy was 100%.⁵ Of note, the US may rely on commercial fractionators located outside the country to manufacture PDMPs which are imported back into the US to meet local need.⁴¹ In 2014, the US collected 66 litres of plasma per 1,000 people which doubled to 113 litre per 1,000 people in 2017. It is estimated that US exported US\$23.6 billion worth of plasma and plasma therapies, representing 1.6% of total US exports by GDP. This amount increased to US\$26 billion in 2018. Many countries are reliant on US supply of plasma for fractionation.¹

Appendix 2. Lists of Associations, Plasma-Derived Medicinal Products (PDMP) Manufacturers, and Private Plasma Collectors

Note that this appendix has not been copy-edited.

Table 6 Examples of Associations Representing Plasma G- US and Europe

Association	Website
European Blood Alliance	http://www.europeanbloodalliance.eu
The European Plasma Alliance (EPA)	http://www.europeanplasmaalliance.eu
The Plasma Protein Therapies Association (PPTA)	http://www.plasma-protein.com

Table 6
Examples of Associations Representing Plasma Collectors and Plasma Fractionators in US and Europe.

Table 7 Examples of Plasma-Derived Medicinal Products (PDMP) Manufacturers

PDMP Manufacturer	Website
Cellular Sciences Inc.	http://www.cellular.com
Cell Products Laboratory	http://www.cellprod.com
CellPro	http://www.cellpro.com
CellPro Biotech	http://www.cellprobiotech.com
CellPro BioPharmaceuticals	http://www.cellprobiopharma.com
CellPro Bio	http://www.cellprobio.com

Table 7
Examples of Plasma-Derived Medicinal Products (PDMP) Manufacturers or Plasma Fractionators.

Table 8 Examples of Private Plasma Collectors

Private plasma collector	Website
Acute Plasma LLC	http://www.acuteplasma.com
B Positive Plasma LLC	http://www.bpositiveplasma.com
BlueLife Plasma Services LP (BlueLife)	http://www.bluelifeplasma.com
Donor US LLC (donorUS)	http://www.donorus.com
Donor 90	http://www.donor90.com
Donor Pharmaceuticals	http://www.donorpharm.com
DPH Plasma Inc.	http://www.dphplasma.com

Table 8
Examples of Private Plasma Collectors.