

BACKGROUND DOCUMENT | MAY 29, 2013

ISSUE

Canadian Plasma Resources is proposing to open plasmapheresis operations to collect plasma from paid donors in Ontario. Questions are being raised around safety, supply, ethics, the lack of public consultation and the eventual impact on the voluntary non-paid systems operated by Canadian Blood Services (CBS) and Héma-Québec. The federal Minister of Health announced on March 11, 2013 that Health Canada would seek the views of individuals and organizations that are interested in this issue. (This background document informs the *Canadian Hemophilia Society (CHS) Policy on Paid Plasma Donations*.)

THE LEGAL ENVIRONMENT

The Quebec Civil Code prohibits the commercialization of cells, tissues and organs, including blood. There is no such legal or regulatory prohibition in the rest of Canada. Private companies can legally collect plasma from paid donors for the manufacture of medicinal products under the regulation of Health Canada.

Cangene has been operating a plasma collection facility in Winnipeg for many years under the strict regulation of Health Canada and the U.S. Food and Drug Administration (FDA). Donors are paid. The plasma is used in their own manufacturing facility to make purified, concentrated antibody preparations (hyperimmunes) with target applications in infectious disease, hematology, transplantation and biodefence for the world market.

THE HISTORY

The Commission of Inquiry on the Blood System in Canada (Krever Commission) recommended in its 1997 report that blood and blood products be collected from voluntary, non-paid donors, except in special circumstances¹. The Commission was created because about 1200 Canadians, including 700 people with bleeding disorders, were infected with HIV through blood and blood products in the late 1970s and 1980s at a time when donor screening, donor testing and viral inactivation were either absent or deficient. Another 20,000 Canadians, including 1600 people with bleeding disorders, were infected with hepatitis C before 1990.

The Krever Commission found that the Canadian blood system responded poorly to pathogens entering the blood system. Problems included a lack of regulation by Health Canada, a rigid and unresponsive decision-making process at the Canadian Red Cross, delays in introducing donor screening and testing, profits taking priority over safety for the

¹ *Commission of Inquiry on the Blood System in Canada*, Final Report, Volume 3, page 1047, 1997

manufacturers of blood products, delays in the removal of unsafe products when safe products were available, collection of blood in unsafe locations such as prisons and failure of the provinces and territories to fund urgent blood safety measures in a timely manner. Given the important role played by paid plasma donations collected in unsafe U.S. locations in transmitting infections in the 1970s and 80s, patients are understandably concerned today.

In the United States, the Institute of Medicine report in 1995 found similar inadequacies².

Viral pathogens—primarily HIV, HBV and HCV—were transmitted almost entirely by fresh blood components (red cells, platelets, plasma for transfusion and cryoprecipitate) and clotting factor concentrates (factor VIII and IX) for the treatment of hemophilia. The last viral known viral transmission of HIV through hemophilia products in Canada occurred in 1987; the last HCV transmission in 1988.

In the mid and late 1980s, physicians and patients in the hemophilia community in Canada came together to demand safe products and a more accountable blood system. This culminated in Canada with the 1993-97 Commission of Inquiry and the creation in 1998 of two blood establishments—Canadian Blood Services and Héma-Québec—to replace the Canadian Red Cross.

Major technological advances occurred in the wake of the tainted blood tragedy. Successive generations of ELISA antibody tests for HIV (1985) and HCV (1990) reduced the number of infected donations entering the blood supply. The addition of the HIV p24 antigen test in the mid-1990s and nucleic amplification tests (NAT) in the 2000s reduced the window periods during which a donor was potentially infectious to, for example, 12 days for HIV. While not perfect, the combination of effective donor screening and sensitive testing resulted in transmissions through fresh blood components becoming a rarity. No transmissions of HIV have occurred with red cells, platelets or plasma in the 15-year history of CBS and Héma-Québec.

An even greater advance for plasma-derived products was the development of viral reduction procedures, applied during the manufacturing process according to strict Good Manufacturing Practices. These techniques were first introduced in the mid 1980s and then refined over the next decades. They include solvent detergent treatment, heat and filtration. Most plasma-derived products are virally attenuated through two distinct processes. Viral reduction technologies are the single most important factor in the safety of these products and are primarily responsible for the perfect 20-year safety record with regard to HIV, HCV and HBV. These procedures, however, cannot yet be applied to fresh blood components³.

Manufacturers of plasma-derived products developed a host of other safety measures through voluntary industry standards that surpass Health Canada and FDA regulations. These include a quarantine of first-time plasma donations until a second donation has proven negative for all pathogens, an inventory hold on plasma to allow for post-donation information to be known, and NAT testing for five viruses—HIV, HBV, HCV, hepatitis A and parvovirus B19—not only on individual donations but also on pools of plasma. **Plasma-derived products manufactured following Standard Operating Procedures and Good Manufacturing Practices are of equally high quality from both paid and non-paid donors.**

² *HIV and the Blood Supply: An Analysis of Crisis Decision making*. 1995. Washington, DC: National Academy Press

³ The epidemiology of virus transmission by plasma derivatives: clinical studies verifying the lack of transmission of hepatitis B and C viruses and HIV type 1. E Tabor. *TRANSFUSION* 1999;39:1160-1168

Another breakthrough was the development of recombinant (genetically engineered) clotting factor concentrates for hemophilia A (1994), hemophilia B (1997) and factor XIII deficiency (2012).

Regulatory authorities such as the U.S. FDA and Health Canada were severely criticized for their laxness in the 1980s. Both bodies increased their capacity to oversee blood establishments, blood and plasma collection sites and pharmaceutical manufacturing facilities, and introduced strict guidance documents related to donor selection and testing.

The world has changed since the 1980s. Thanks to the Internet, communications are instantaneous. News about emerging and potentially blood-borne infections over the last 15 years—vCJD, West Nile Virus, SARS, dengue fever, Chagas disease, chikungunya, hepatitis E and G, babesia microti, HHV-8, Leishmania, Q fever, spumavirus, XMRV...) goes around the world in minutes and becomes the subject of intense study and debate as to their transmissibility through fresh blood components and plasma-derived products, and possible mitigation measures. Gone are the “wait-and-see” days of the 1980s.

Of the pathogens listed above, only vCJD, a prion and not a viral pathogen, seems to have eluded viral elimination technologies in plasma-derived products. One case of vCJD transmission through factor VIII may have occurred in the U.K.⁴ This factor VIII product was made from voluntary, non-paid donors.

No donor screening or testing existed for the other pathogens listed above, yet none infected plasma products. Why? Either they were not transmissible by plasma or they were eliminated by viral reduction technology.

PATIENT SAFETY

The safety of blood, blood products and their alternatives for the recipient is paramount in the donor selection process.

Both blood establishments and the plasma industry operate within stringent national, regional and international regulatory regimes—U.S. FDA, European Medicines Agency, Health Canada, World Health Organization (WHO)— that support the safe and effective collection and provision of fresh blood components and plasma-derived products.

The production processes used to produce fresh blood components and plasma-derived products involve different manufacturing pathways and take advantage of different risk mitigation measures. Table 1 shows some examples.

⁴ Variant Creutzfeldt-Jakob disease. Ironside JW. National Creutzfeldt-Jakob Disease Surveillance Unit, Division of Pathology, School of Molecular and Clinical Medicine, University of Edinburg. *Haemophilia*. 2010 Jul;16 Suppl 5:175-80.doi:10.1111/j.1365-2516.2010.02317.x.

TABLE 1

Safety measures	Applicable to fresh blood components	Applicable to plasma-derived products
Rigorous donor selection (health status, risk behaviours, travel, etc.)	Yes	Yes
Inventory holds for first-time donors (First-time donors donate once to qualify, then return a second time; after all TTI markers are negative on the second donation, the first donation is used)	No	Yes
Third-generation ELISA antibody testing	Yes	Yes
NAT testing for HIV, HBV and HCV on individual donations	Yes	Yes
PCR testing for HAV, parvovirus B19	No	Yes
Fractionation industry standards for accepting plasma (International Quality Plasma Program)	No	Yes
Dual viral elimination/reduction methods (solvent detergent, heat, or filtration) for finished products	No	Yes
NAT testing on mini-pools of donations	Yes	Yes
Patients followed closely to ensure safety of product	Yes	Yes
Donor records computerized for better vein-to-vein tracking	Yes	Yes
Well-characterized Standard Operating Procedures for collection facilities	Yes	Yes
Regulatory authorities trained and experienced in inspection procedures of collection facilities	Yes	Yes

As a result of these different risk mitigation strategies available to the two sectors, plasma-derived products from paid plasma donors have proven safer than fresh blood components from non-paid donors, largely because of the viral attenuation steps applied to plasma products. No transmissions of HIV, HBV, or HCV are known to have occurred in the last 20 years with plasma-derived products manufactured in a well-regulated GMP environment. **The collection of source plasma from paid donors in a properly regulated environment is not a patient safety issue⁵.**

A very small number of HIV, HBV, and HCV infections have occurred through fresh blood components in North America in the last decade.

Monitoring, nevertheless, remains critical. **Any endeavour to collect plasma for plasma-derived products from paid donors in Canada must respect the highest regulatory standards. Health Canada should make these standards known to Canadians and report to Canadians on a regular basis the results of their collection site inspections, including transfusion-transmissible infection rates among donors. The regulator should be monitored and held to account.**

⁵ CPMP Position Statement: Non-remunerated and remunerated donors: safety and supply of plasma-derived medicinal products. The European Agency for the Evaluation of Medicinal Products. London, 30 may 2002. EMEA/CPMP/BWP/1818/02/Final.

SUPPLY AND DEMAND

Plasma-derived products in adequate supply from both paid and non-paid sources are essential to the health of thousands of Canadians and, indeed, hundreds of thousands of people around the world.

The Canadian blood establishments, Canadian Blood Services and Héma-Québec, meet 100% of the demand for the supply of fresh blood components—red cells, platelets and plasma for transfusion—in Canadian hospitals. In addition, surplus plasma from these non-paid donors, both recovered and source, is sent to Grifols in Europe and CSL Behring in the U.S. for manufacture into plasma-derived products such as immune globulins, albumin and factor VIII/von Willebrand factor for the Canadian market. This situation is identical to that in the U.S. where the American Red Cross, America's Blood Centers and other not-for-profit blood establishments supply all American hospitals with fresh components from non-paid whole blood, platelet and plasma donors. In the U.S., surplus recovered plasma is sold to commercial fractionators for manufacture into plasma-derived products.

The world, however, has changed since the 1990s in terms of the demand for plasma-derived products. While Canadian Blood Services and Héma-Québec could reasonably imagine supplying the plasma for fractionation to meet the demand for these products in 1997, when the Commission of Inquiry made its findings, such is not the case today.

In the 1980s, factor VIII for the treatment of hemophilia A was the product that drove the plasma business. That changed with the advent of recombinant factor VIII. Immune globulin (Ig), a life-saving treatment for a variety of immunologic disorders, became the demand driver among plasma-derived products. CBS and H-Q collect 27% and 11% respectively of the plasma needed to manufacture Ig for Canadian needs. This level of sufficiency is decreasing yearly as the demand for Ig grows faster than the increase in surplus plasma from Canadian sources. A very small amount of U.S. recovered plasma from non-paid donors is now being purchased by CBS to augment the quantity of plasma sent to the toll fractionators, Grifols and CSL Behring. Thus, close to 80% of Canadian Ig needs are currently met by the purchase of commercial Ig from for-profit fractionators. Almost all of the plasma they use is from voluntary, paid donors in the U.S.

Health Canada does not allow the import of plasma-derived products made from European plasma (paid or not) because of concerns over vCJD.

Nor are CBS and H-Q able to supply enough plasma for the Canadian requirements in albumin, though the shortfall is less dramatic.

Many clotting factors to treat inherited bleeding disorders are made from U.S. paid donor plasma. There is one exception. Since 2011, the factor VIII/von Willebrand (FVIII/VWF) product, Humate P[®], manufactured by CSL Behring for the treatment of von Willebrand disease, a common bleeding disorder, has been made from CBS plasma. Another FVIII/VWF product, Wilate[®], manufactured by Octapharma and used for both VWD and hemophilia A, is made from U.S. source plasma from paid donors. In Quebec, Humate P[®] will be made from Héma-Québec plasma starting in 2013 or 2014. Humate P[®] accounts for about 75% of the FVIII/VWF market; Wilate[®] 25%. All other plasma-derived factor concentrates (factors I, FII, FVII, FX, FXI, FXIII) to treat rare bleeding disorders are made from the plasma of paid U.S. donors.

Other life-saving plasma-derived products such as C1 esterase inhibitor for the treatment of hereditary angioedema, alpha 1 antitrypsin for the treatment of alpha 1 antitrypsin deficiency and solvent-detergent-treated plasma for a variety of indications are also made from the plasma of paid U.S. donors.

While some European countries are more successful than Canada in plasma collection from non-paid donors, no country is self-sufficient. All rely to some extent on plasma-derived products manufactured from the plasma of paid U.S. donors.

Plasma and plasma-derived products are a global industry. Germany, Austria and the Czech Republic have in the past ten years begun plasma collection operations with paid donors. The not-for-profit sectors in those countries continue to supply fresh blood components from non-paid donors.

Canada, U.S. and other developed countries are identical in being self-sufficient in fresh blood components from non-paid donors, and almost totally reliant for the supply of plasma-derived products on U.S. paid donors.

There are currently no serious strategies in place around the world to reverse this situation. The demand for life-saving plasma-derived products is increasing faster than the growth in whole blood collection (and therefore recovered plasma). Not-for-profit blood establishments do not consider it economical to recruit non-paid donors for a self-sufficient supply of plasma for plasma-derived products; they choose to rely on the highly efficient for-profit global plasma collection and fractionation industries. Therefore the reliance on source plasma from paid donors will only increase.

In the absence of any realistic strategy to significantly increase the Canadian contribution to the world supply from non-paid donations, and when Canada relies almost entirely on paid donors from the U.S. for life-saving plasma-derived products, it is not defensible to reject paid donor practices on ethical grounds.

The 2012 Dublin Consensus Statement focused on the supply of plasma-derived products and included these statements:

- Recognise that plasma and plasma-derived medicinal products supply are basic healthcare needs and a safety issue, mainly depending on accessibility and affordability for health care systems. An insufficient supply is a major safety risk to patients.
- Promote national and regional approaches to the development of solutions suitable for their differing healthcare environments.
- Recognise that both private and public sectors are needed to meet global demand for plasma derived products in line with the Dublin Consensus (2011).⁶

The World Health Organization promotes the development of national blood collection systems based on non-paid donations. This makes perfect sense in a world where many developing and emerging countries do not have adequate supplies of safe fresh blood components. The WHO dream of using the recovered plasma from these whole blood donations to supply the plasma for fractionation for plasma-derived products is decades away from realization. In the meantime, WHO policies on non-remuneration should not have

⁶ The Dublin Consensus Statement 2011 on vital issues relating to the collection and provision of blood components and plasma-derived medicinal products. B. O'Mahony and A. Turner. Vox Sanguinis, 2011 International Society of Blood Transfusion DOI: 10.1111/j.1423-0410.2011.01528.x.

the unintended consequence of reducing the world's supply of life-saving plasma-derived products.

CBS and Héma-Québec should make all reasonable efforts to increase the quantity of Canadian plasma for fractionation from non-paid donors and the number and quantity of plasma-derived products made from this plasma. However, thousands of people in Canada and hundreds of thousands of people around the world will continue to rely on plasma-derived products from paid donors for their health and their lives.

PEACEFUL COEXISTENCE OF THE TWO SECTORS

There is concern that the presence of two independent collection systems, one for fresh blood components and one for source plasma for fractionation, in the same region or country, could create a risk of shortage in supply of fresh blood components. Co-operation between blood establishments and the plasma industry is important to ensure that the best community outcomes are achieved including sufficiency of supply for all patients.

Any endeavour to collect plasma for plasma-derived products from paid donors must not affect the ability of Canadian Blood Services or Héma-Québec to collect whole blood, platelets and plasma from non-paid donors to meet the needs for fresh blood components. Canadian Blood Services and Héma-Québec should report to Canadians on a regular basis the impact of paid plasma collections on their ability to meet the needs of Canadian patients.

Similarly, activities undertaken to provide adequate supplies of blood components should take into account the ability of those who collect plasma for fractionation to meet the requirements of patients who rely on these therapies.

DONORS

Blood establishments, the plasma industry and society in general should highly value all those who donate blood or plasma for the benefit of patients and recognize that donors perform a good deed and treat donors with respect.

The health of donors, paid or non-paid, should not be compromised by their donations. Donors should not be exploited by any individual or organization. Measures and initiatives taken to encourage blood and plasma donations should not overwhelm the capacity of the donor to make an informed decision about whether to donate.

THE PATIENT PERSPECTIVE

The ultimate purpose of blood and plasma donation is to improve the health of patients and save lives. Consequently, the patient perspective needs to be heard.

Patients whose continued health is dependent on the use of blood components or plasma-derived products have a right, through their representative organizations, to be consulted on any issue which may have an impact on the safety, efficacy or supply of the treatment they receive. Health authorities should ensure that robust mechanisms are in place to ensure that this happens.

APPENDIX 1: DEFINITIONS

Blood establishments – Not-for-profit entities that collect whole blood, platelets and plasma from voluntary non-paid donors for use in hospitals. Surplus plasma is sent for fractionation into plasma-derived products. The blood establishments in Canada are Canadian Blood Services and Héma-Québec.

The plasma industry – For-profit entities that collect source plasma from voluntary paid donors for fractionation and manufacture into plasma-derived products such as immune globulins, albumin, factor VIII, factor IX, C1 esterase inhibitor, alpha 1 antitrypsin, solvent-detergent-treated plasma and many others.

Plasma – (Blood) plasma is the pale yellow liquid component of blood that normally holds the blood cells in whole blood in suspension. It makes up about 55% of total blood volume. It is mostly water (93% by volume), and contains dissolved proteins such as albumins, globulins, fibrinogen, glucose and clotting factors.

Fractionation – The process whereby plasma is separated into its constituent proteins. This is done in a highly regulated pharmaceutical environment.

Fresh blood components – Red cells, platelets and plasma for transfusion.

Plasma-derived products – Plasma protein products manufactured by companies in the pharmaceutical industry. They include immune globulins, albumin, factor VIII, factor IX, C1 esterase inhibitor, alpha 1 antitrypsin, solvent-detergent-treated plasma and many others.

Recovered plasma – The plasma that is separated from whole blood donations from voluntary, non-paid donors.

Source plasma – The plasma that is collected through plasmapheresis from both paid and non-paid donors.

Voluntary donation – A whole blood or plasma donation that is freely given without coercion.

Paid donation – A plasma donation for which there is remuneration in the form of money, goods or services, reimbursement of travel costs, payment of meals or time off work to allow donation.