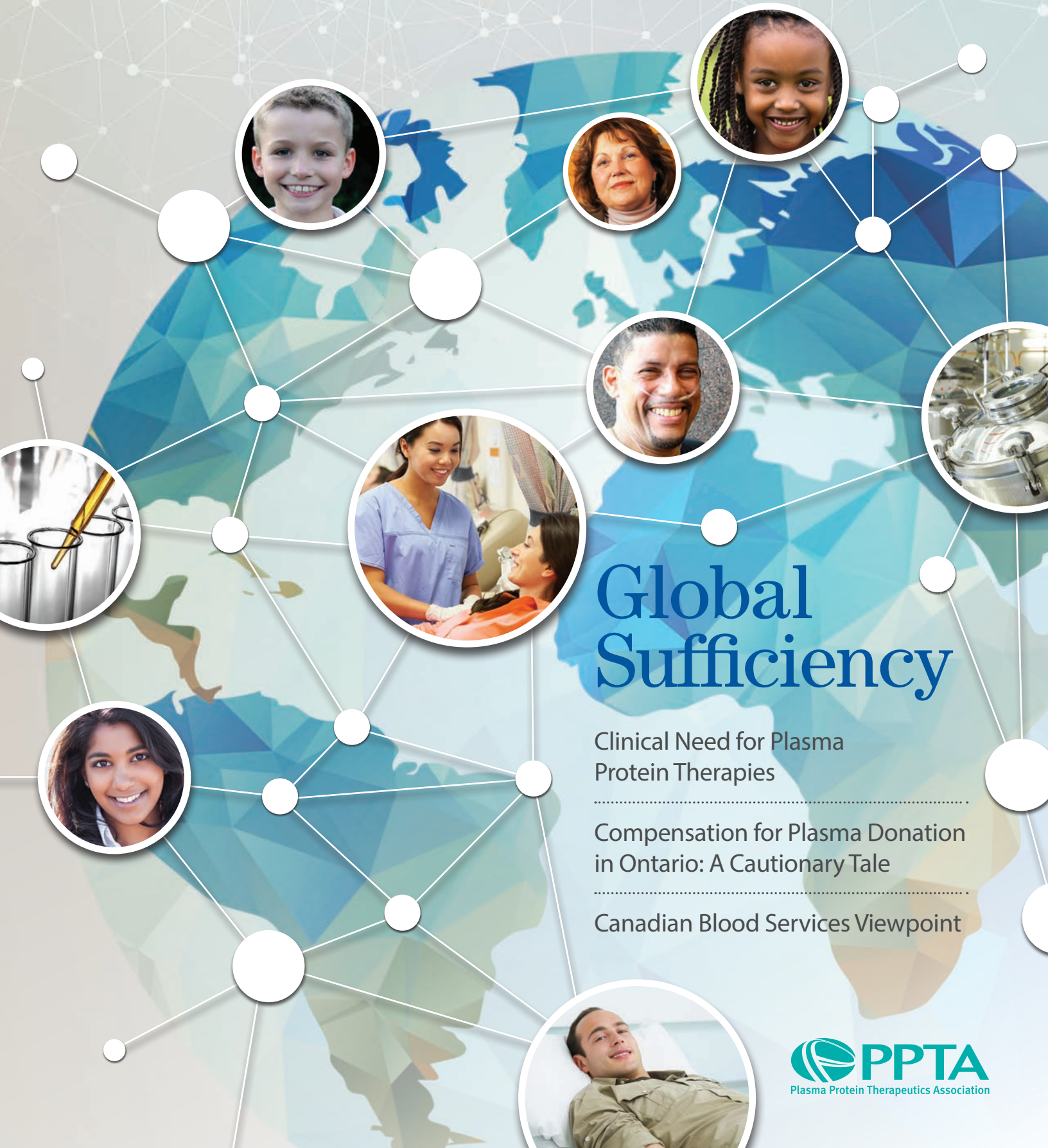
THE SOURCE

MAGAZINE OF THE PLASMA PROTEIN THERAPEUTICS INDUSTRY

FALL 2014



Global Sufficiency

Clinical Need for Plasma Protein Therapies

Compensation for Plasma Donation in Ontario: A Cautionary Tale

Canadian Blood Services Viewpoint

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In My View

BY JAN M. BULT, PRESIDENT & CEO

This industry is grateful to the many donors who donate their valuable plasma to help so many patients in the world whose lives depend on the (often) lifesaving therapies that our members manufacture from the precious plasma that is donated. Today I want to write about the patients whose lives are many times saved because of the use of albumin and the medical experts who are involved in their treatment.

In October 2013, a "High Level Policy Makers Forum" was held in Rome, Italy that resulted in the development of "The Rome Declaration on Achieving Self-Sufficiency in Safe Blood and Blood Products based on Voluntary Non-Remunerated Donation (VNRD)."

This Declaration [carrying the World Health Organization (WHO) logo] stated: "We being 153 representatives of ministries of health, national blood programmes, national blood transfusion services, national public health agencies, national regulatory bodies, national plasma fractionation institutes, representatives of international, intergovernmental and nongovernmental organizations, and experts in transfusion medicine from 51 countries from all WHO regions participated in the WHO High-Level Policy Makers Forum on Achieving Self-Sufficiency in Safe Blood and Blood Products, based on Voluntary Non Remunerated Donation, held on October 8-9 in Rome, Italy. This Forum was organized jointly by the World Health Organization, the Ministry of Health, Italy, and the Ministry of Health, Labor and Welfare, Japan, in collaboration with the Council of Europe, European Commission, International Federation of Red Cross and Red Crescent Societies, International Society of Blood Transfusion, International Federation of Blood Donor Organizations and European Blood Alliance."

This Declaration contains endorsements and calls on national authorities to:

- **"Introduce legislation to prohibit payments in cash or in kind for the donation of blood, plasma and other blood components and also, with specific timelines, to ensure VNRD as the source of labile blood components and Plasma Derived Medicinal Products (PDMP) as a means of moving towards self-sufficiency in safe blood and blood products**
- **Provide sufficient financial and other resources to move towards self-sufficiency based on VNRD**
- **Incorporate measures to achieve self-sufficiency into the regulatory framework; to facilitate the supply of plasma, intermediate products and PDMP sourced from VNRD within regional or other collaborative self-sufficiency arrangements, including contract fractionation; and to phase out in a programmed manner, the use of blood components for transfusion, intermediates and PDMP obtained from paid or compensated donors and family/ replacement donors."**

There were many other statements included in the document. The above mentioned items are examples of measures (when adopted) which will have a devastating impact of the lives of many patients globally who depend on the life-saving therapies that are manufactured by the private sector manufacturers.

There are many problems with this Declaration. Multiple organizations, including PPTA have contacted the WHO to express their concerns. At the meeting where this Declaration was discussed, there was no participation of various stakeholders whose voice should have been heard such as:

- **Patients who depend on these therapies**
- **Regulatory agencies who regulate the plasma protein therapies**
- **Countries that collect plasma from compensated donors**
- **Private sector industry**

In a response to PPTA, the WHO clarified that:

- **The Declaration was not endorsed by the WHO.**
- **The WHO logo was removed.**
- **The disclaimer was amended to state that the content of declaration does not necessarily represent the views of the Organization.**

Not only PPTA, but very importantly, patient organizations wrote strong letters to the WHO as well. PLUS (Platform of Plasma Protein Users) in Europe wrote:

"There are several recommendations in the Rome Declaration that would, if implemented, seriously reduce the supply of plasma derived medicinal products and put patient's life at risk. We also strongly believe that the drafting process of the Rome Declaration is fundamentally flawed given that patient organisations who are directly concerned by this issue were not consulted and were excluded from this process."

The American Plasma Users Coalition (APLUS) represents 11 U.S. based patient organizations also wrote a letter:

"APLUS is also quite disturbed and appalled that the drafting process of the Rome Declaration excluded patients and patient organizations. Patient organizations have a right to represent and speak for the collective interests of those who will be affected by the policies of governments. At this time when patient centered health care is a driving force in health care policies, patients and their organizations must be involved at the very beginning of the policy making process. The legitimacy of policies which are not derived from equitable patient representation in the policy making process are called into severe question."

Another strong letter came from the International Plasma Fractionation Association (IPFA). IPFA represents the public sector manufacturers.

"IPFA has serious reservations concerning the proposed call to relevant authorities to introduce legislation to prohibit payment in cash or in kind to the donation of blood, plasma and other blood components…This call is unrealistic and would have serious consequences if adopted and implemented. The global supply of plasma would be severely disrupted and for many patients the secure and sufficient supply of PDMP would cease because existing blood establishments (in both developed and developing countries) are and will not be able to compensate for the huge amount of plasma lost from current paid plasma sources.

IPFA is equally concerned about the proposed call to relevant authorities 'to phase out in a programmed manner…intermediates and PDMP obtained from paid or compensated donations and family/replacement donors.' In the absence of alternative solutions to replace current volumes of paid plasma with plasma from voluntary, non-remunerated blood donation (VNRBD), and implemented on a local, regional and global scale, any policy which would endanger PDMP supplies to dependent patients cannot and should not be endorsed."

As can be seen in these letters, there are many concerns expressed and it is important to put some reality into this discussion.

Collecting whole blood for transfusion is a national issue and nobody would argue against setting up national organizations to collect sufficient whole blood and/or components to provide to patients in a hospital setting. Nobody will argue against national self-sufficiency for whole blood.

However, the manufacture of plasma protein therapies is very complex and costly. Many countries (e.g. Norway, Finland, Denmark, Scotland, England, Switzerland to name a few) have given up their national fractionation activities because of that. To call for national self-sufficiency for plasma protein therapies is unrealistic and (with very few exceptions) cannot be achieved. We are living in a global world and the sufficiency of regulated plasma protein therapies is a global issue.

It is time to separate questions related to whole blood from questions related to plasma for fractionation and the plasma protein therapies derived from that plasma. There is a world of difference between these two issues. Many of the discussions around the supply of therapies are political instead of driven by patient need.

We listen to the patients and their needs. It is time that everyone does that. •

Jan M. Bult, *President & CEO*

Clinical Need for PLASMA PROTEIN THERAPIES

BY PROFESSOR ALBERT FARRUGIA

Given the current status of immunoglobulin (Ig) as the plasma procurement driver, a key element is the need for Ig therapies. Ig usage varies greatly between countries with a similar health care status [*Figure 1*, extracted from Robert (2011)]. This feature has contributed to a debate around the appropriateness of Ig, with some questioning the high usage in some countries as a manifestation of wastage (Rossi et al 2011).

It should be noted that therapeutic claims for this product, as with all plasma protein therapies (PPTs), have to be approved by regulators through evidence before it is put on the market, and increasingly, product reimbursement and hence, usage, is based on such approved claims. In reimbursement systems where a strict evidence base is used to ensure distribution of product, an examination of usage may be instructive. In two high-consuming countries—the U.S. and Australia—the main indications for Ig are assigned by the respective bodies producing professional guidelines and are reflected in the usage (Orange et al 2006, Australian National Blood Authority 2012). Variations in usage may ensue from differences in dosage protocols, diagnosed prevalence and reimbursement pathways , but an assessment of evidence-based clinical demand may be performed using the available data and modelled for the uncertainty around the relevant parameters using decision analysis (Stonebraker et al 2014). Such an exercise estimates the latent therapeutic demand for Ig in the two most common immunodeficiency disorders to be 72 g per 1000 population. This exceeds the total Ig consumption across all indications in several European countries [*Figure 2*], and also exceeds the estimated consumption for these specific primary immunodeficiency diseases in the U.S. It should be noted that these diseases absorb only 20 to 30 % of current Ig usage. We conclude that there is little evidence that Ig usage is not reflective of real, evidence-based medical need, and that, if anything, clinical need exceeds the current levels observed, even in high usage countries.

The clinical need for other PPTs currently is such that generating a plasma input which satisfies the Ig need will allow production of the other main PPTs to levels addressing current sufficiency. The latent therapeutic demand for Factor VIII for treating haemophilia was estimated at 6.9 International Units (IU) per capita in a study employing decision analysis to model the uncertainty (Stonebraker et al 2004). Current Factor VIII usage in the peer hemophilia treatment countries now exceeds this by a substantial margin (*Figure 3* extracted from World Federation of Hemophilia (2012), as treatment protocols continue to improve and patient populations expand (Farrugia 2013). As much of the expansion in clinical need for Factor VIII demand has been absorbed by the provision of recombinant, rather than plasma derived Factor VIII, Factor VIII is unlikely to reassume its position as a plasma driver.

Albumin's position as a PPT driver product has shrunk considerably over the past thirty years. Estimates of clinical need for albumin are considerably more difficult than for the other main PPTs as this product has been used historically in a diverse range of indications in acute

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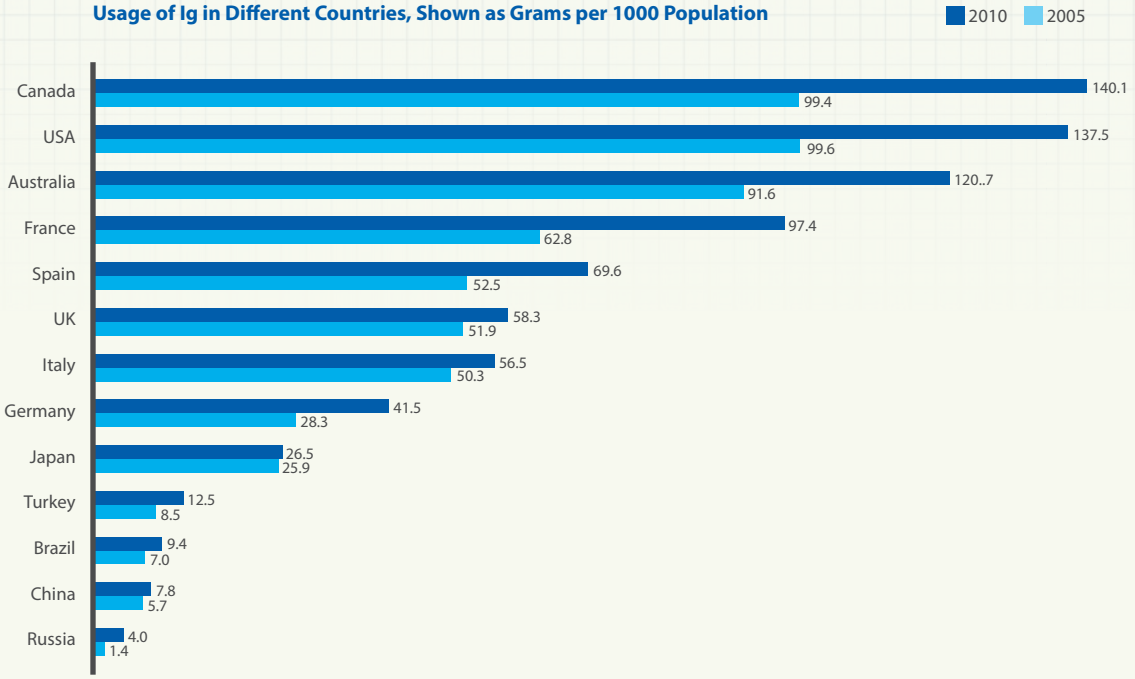
FIGURE 1

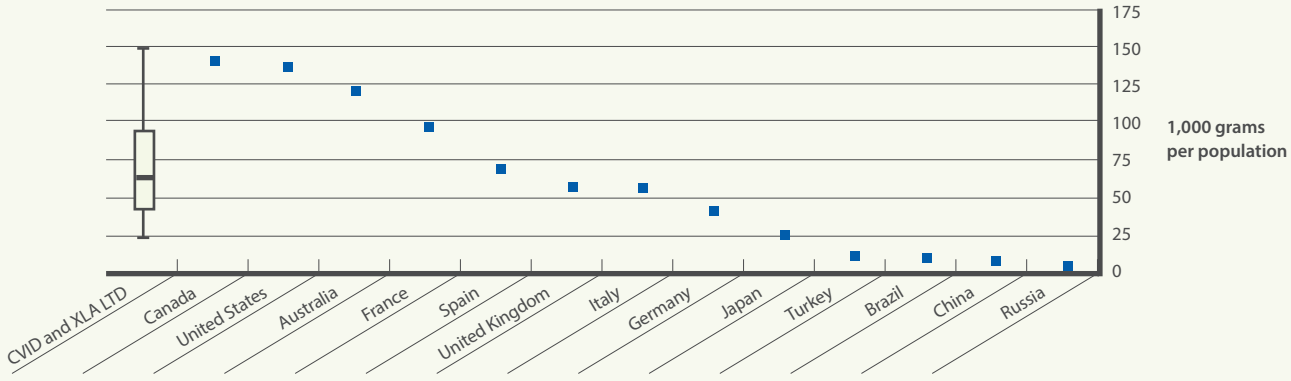
Usage of Ig in Different Countries, Shown as Grams per 1000 Population



From Robert (2011) . IVIG/SCIG: Global Usage Trends. Presented to The IPOPI Global Leaders Meeting 2011, November 4-5, 2011, London, England. Available on http://www.ipopi.org/uploads/Patrick%20Robert.pdf.

FIGURE 2

Total Usage of Ig in Different Countries, Relative to the Latent Therapeutic Demand for Primary Immunodeficiency



From Stonebraker et al (2014) Modeling primary immunodeficiency disease epidemiology and its treatment to estimate latent therapeutic demand for immunoglobulin.J Clin Immunol. Feb;34(2):233-44.

care, rather than in focussed populations of chronic rare disease patients. Its main usage as a blood expander in trauma has been gradually supplemented and supplanted by a range of evidence-based indications drawing on albumin's pharmacological properties (Vincent et al 2014). While estimates for the potential demand from these indications is still accruing, it may be noted that the consumption in the highest usage countries (Vaglio et al 2013) can be easily met through fractionation of the plasma needed to extract a sufficiency of Ig.

In summary, the clinical need for the main PPTs is structured around a number of evidence-based indications approved for marketing and reimbursement. Ig is the current predominant PPT, and plasma requirements are shaped by the clinical need for Ig. The fractionation process' capacity to extract the other products without affecting the yields of the individual proteins significantly results in the capacity to extract Factor VIII and albumin to levels similar to what is required. •

PROFESSOR ALBERT FARRUGIA, *PPTA Vice President, Global Access*

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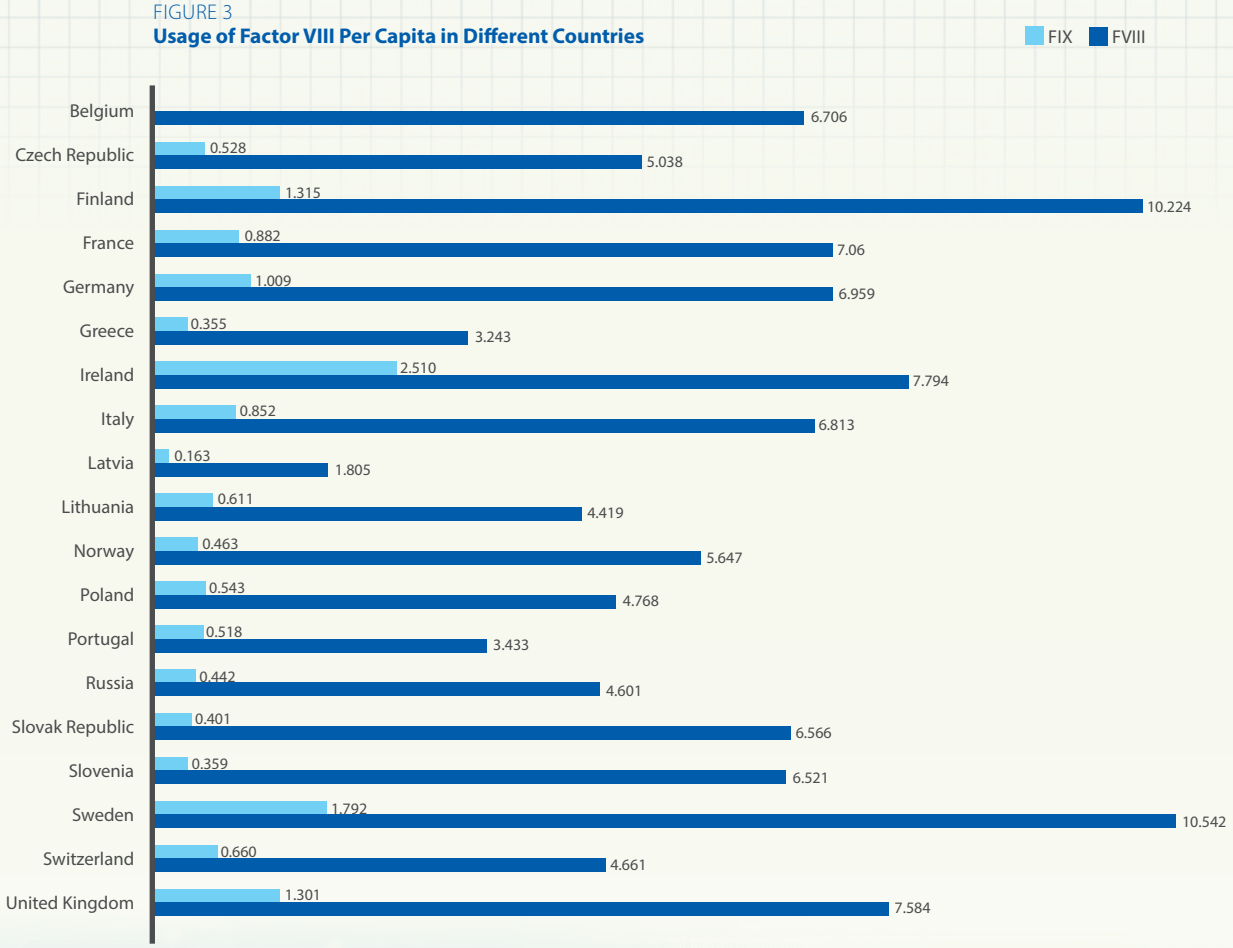
FIGURE 3

Usage of Factor VIII Per Capita in Different Countries



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Compensation for Plasma Donation in Ontario: A CAUTIONARY TALE

BY DAVID PAGE

In July 2014, the Government of Ontario re-introduced legislation to prohibit payment for donation of whole blood and blood constituents in that Canadian province. The proposed Bill came after more than a year of public controversy over the planned opening of three plasma collection centres by Canadian Plasma Resources (CPR) in Toronto and nearby Hamilton. The legislation will be debated and likely passed by the Legislative Assembly this autumn.

In Canada, regulation, licensing, and inspection of blood establishments is a federal responsibility of Health Canada. The agency is currently evaluating the CPR submission to open the three centres. Policy on compensation of donors, however, is up to Canada's ten provinces and three territories. Currently, only one province prohibits payment for blood or plasma donation. Quebec's Civil Code stipulates that the donation of any body part must be made without compensation. In Manitoba, on the other hand, Cangene, purchased in 2014 by Emergent BioSolutions, has been manufacturing a variety of immune globulins from compensated plasma donations for three decades, licensed by both Health Canada and the U.S. Food and Drug Administration (FDA).

Canada is largely dependent on the U.S. for both plasma-derived medicinal products and the plasma required to manufacture them. According to Canadian Blood Services (CBS) and Héma-Québec, the two blood establishments that collect blood from non-compensated donors in the country and that distribute both labile and stable blood products to Canadian hospitals and patients, 27 of the 30 plasma-derived products are made entirely from U.S. plasma. Of the other three, CBS collects only 30% of the plasma needed to manufacture the immune globulins it distributes from non-compensated donors; Héma-Québec only 10%. Nor is Canada self-sufficient in plasma from non-compensated donors for the manufacture of albumin or factor VIII/von Willebrand factor concentrate.

When CBC Television reported on the opening of the three Ontario plasma centres in February 2013, the outcry was immediate. It was led by individuals who had lived through Canada's tainted blood tragedy and the ensuing Royal Commission of Inquiry (the 1993-97 Krever Commission). More than 1000 Canadians were infected with HIV through blood and blood products before 1987, including 700 people with hemophilia through factor concentrates mainly from compensated donors in the U.S. More than 20,000 people were infected with hepatitis C before 1990, the vast majority infected from transfusions from voluntary non-compensated Canadian donors. Many have since died. Government compensation programs for the Canadians affected have cost more than two billion dollars in public funds. The proceedings of the Krever Commission were front page news for years. Its final recommendations changed blood establishments around the world. One of those recommendations was that "donors of blood and plasma should not be paid for their donations, except in rare circumstances."

Soon joining the activists protesting the opening of the centres were physician groups, nurses groups, unions, prominent ethicists, opposition members in the federal

Continued on page 8 >

Parliament, and all parties in the Ontario Legislature. A statement by the Opposition Health critic in Ottawa was typical of the reaction: "In the 1980s, blood from for-profit brokers was a significant contributor to the tainted blood scandal where 20,000 Canadians were infected with HIV and hepatitis C," said New Democratic Party (NDP) Health critic Libby Davies (Vancouver East). "It is our responsibility to ensure that that sad chapter in Canadian history is never repeated."

The concerns of those who wanted to block the opening of the centres were primarily these:

- Paid donors are less safe than non-paid donors;
- Compensating plasma donors will undermine Canada's voluntary donor system;
- It is unethical to pay for a human body part.

In addition, opponents objected to the location of the centres, which, while close to universities, were also next door to homeless shelters or drug rehabilitation centres.

Tension soon grew between the federal government, which had been licensing paid plasma collection centres for decades (Cangene) based on regulations similar to those in the U.S., and the Ontario government, intent on finding a way to block the opening of the centres. The federal Minister of Health initiated a consultative process to collect information and perspectives.

Interestingly, the only groups not jumping on the anti-payment bandwagon were the blood establishments and patient groups whose members rely on plasma-derived medicinal products.

Dr. Graham Sher, chief executive officer of Canadian Blood Services wrote in the Toronto Star, on March 13, 2013: "Prohibiting pay-for-plasma would harm patients. Part of operating a safe system is ensuring security of supply. The reality is that thousands of patients depend on these life-saving fractionated products, and without those produced using plasma from paid donors we would not be able to meet patients' needs ... A prohibition on paying donors for plasma for commercial fractionation use would deny patients access to these products, both here in Canada and around the globe. When lives are at risk, that's simply not an option." Dr. Sher also maintained there was no evidence from countries with both paid and non-paid systems that whole blood and platelet donors would stop donating.

The Canadian Hemophilia Society, whose policy had acknowledged the role of compensation since 2001, wrote in the Toronto Star (March 18, 2013): "Thousands of Canadians with chronic blood disorders rely on plasma products from paid donors for their health and their lives ... These plasma products have a 20-year safety record of never transmitting pathogens like HIV, hepatitis B and hepatitis C... In the 1970s and '80s, blood system authorities ignored the facts, followed accepted dogma and imperiled the lives of thousands. In 2013, decisions should be based on current knowledge, not on misconceptions."

Policy decisions of this nature should not be made without hearing from those who are affected the most by the legislation: that is, the recipients of plasma-derived medicinal products represented by their associations.

Hereditary Angioedema Canada published its position on March 20, 2013: "HAE Canada shares the stated positions of the Canadian Blood Services and the Canadian Hemophilia Society that support the long-held practice of using plasma products that were sourced from paid blood donors in treatment of rare blood disorders. HAE Canada considers these products safe and essential."

The debate has raged on in Ontario now for more than a year. Strangely, the draft Bill exempts Canadian Blood Services, presumably because CBS offers "incentives" to donors, and passage of the Bill could threaten the importation of products from paid donors, which would be catastrophic.

Ironically, in Quebec in 2014, where payment is banned, the Government announced an agreement with a fractionator whereby it would provide generous subsidies and loan guarantees to build a plant using U.S. compensated plasma. The Ontario Government itself had only two years earlier promised subsidies to attract a major fractionator to the province. The project fell through.

Patient groups continue to express their objection to the proposed legislation. In July 2014, the Network of Rare Blood Disorder Organizations (NRBDO), a coalition of more than ten associations whose members use blood and plasma products, wrote to the Ontario Minister of Health. The letter said: "There is merit in contributing to the world supply of plasma for the production of plasma derived medicinal products. Global over-reliance on the U.S. plasma supply is risky ... Paying Ontarians is no more or less ethical than paying Americans, as we do today for almost all products used in Ontario and elsewhere in Canada ... Policy decisions of this nature should not be made without hearing from those who are affected the most by the legislation: that is, the recipients of plasma-derived medicinal products represented by their associations."

The NRBDO will appear before the Social Policy Committee studying the draft legislation this autumn. ●

DAVID PAGE, *National Executive Director, Canadian Hemophilia Society*

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Plasma as a Starting Material

BY SONIA BALBONI

When thinking of self-sufficiency in the plasma industry, consider that there are two distinct measures. On the one hand, there is a country's self-sufficiency in its ability to provide plasma protein therapies (PPTs) to all residents who need them. On the other hand, there is a country's self-sufficiency in terms of its available supply of plasma collected in the country for manufacture.

The former measure has been reviewed in discussions by other authors. For the latter, however, the majority of countries that can provide sufficient PPTs to meet the needs of their resident patients do not have self-sufficiency in their domestic plasma supply. There is a global need for plasma for the manufacture of PPTs. This plasma is safe and it is ethically collected.

NEED FOR PLASMA AS A STARTING MATERIAL

Plasma used as a starting material for the manufacture of PPTs is collected from countries around the world and manufactured by companies for distribution globally. The vast majority of this plasma for the manufacture of PPTs is collected in over 450 collection centers in the United States and Europe. (Plasma collected at these centers is termed "source plasma"). Most of the world's plasma is collected in the United States, and a significant amount is also collected in Europe. The plasma collected in the United States is used for manufacture of products that may be marketed throughout

the world; however risk assessments generated by variant Creutzfeldt-Jakob Disease (vCJD) fears have resulted in some government policies that restrict the acceptance of plasma collected in Europe. Many countries do not allow compensation for collection of plasma in general within their borders, for political reasons as discussed elsewhere in this publication. These prohibitions ultimately lead to restrictions on access to plasma for use as a starting material. Therefore, to make up for the lack of plasma available in a country, most European countries import plasma from the United States, or PPTs from the United States and other countries.

The web of production is fluid, and plasma or intermediates manufactured from plasma may pass through various collection, holding and manufacturing sites, in different jurisdictions and countries, before the manufacturing chain is completed. For example, plasma collected in the Southeast (United States) may be transferred to the Midwest, where it can be held for a time as a safety step (i.e. inventory hold). It could then be shipped to the West Coast for initial manufacturing, where certain proteins are extracted for the manufacture of, let's say, Factor VIII to treat a hemophiliac. The remaining fractions might then be sent to another country, Germany, for example, where other proteins are extracted for the manufacture of additional products, including IVIG to treat immune disorders, and albumin to treat trauma patients. Many classes of plasma protein therapies are in production today. Therapies from the same plasma collected at just one center can be manufactured in up to five different sites spanning two continents and three different countries.

PLASMA COLLECTION METHODS

Plasma is collected in various ways and used for a number of life-saving treatments. Plasma used for commercial manufacture of PPTs is never transfused directly into patients, is always pooled, and as an added safety measure, is always required to be held for at least sixty days prior to pooling.

Two distinct methods of collecting plasma are available: source plasma and recovered plasma. From a safety perspective, both methods are acceptable to commercial manufacturers of PPTs, although primarily Source plasma is used in PPT manufacture.

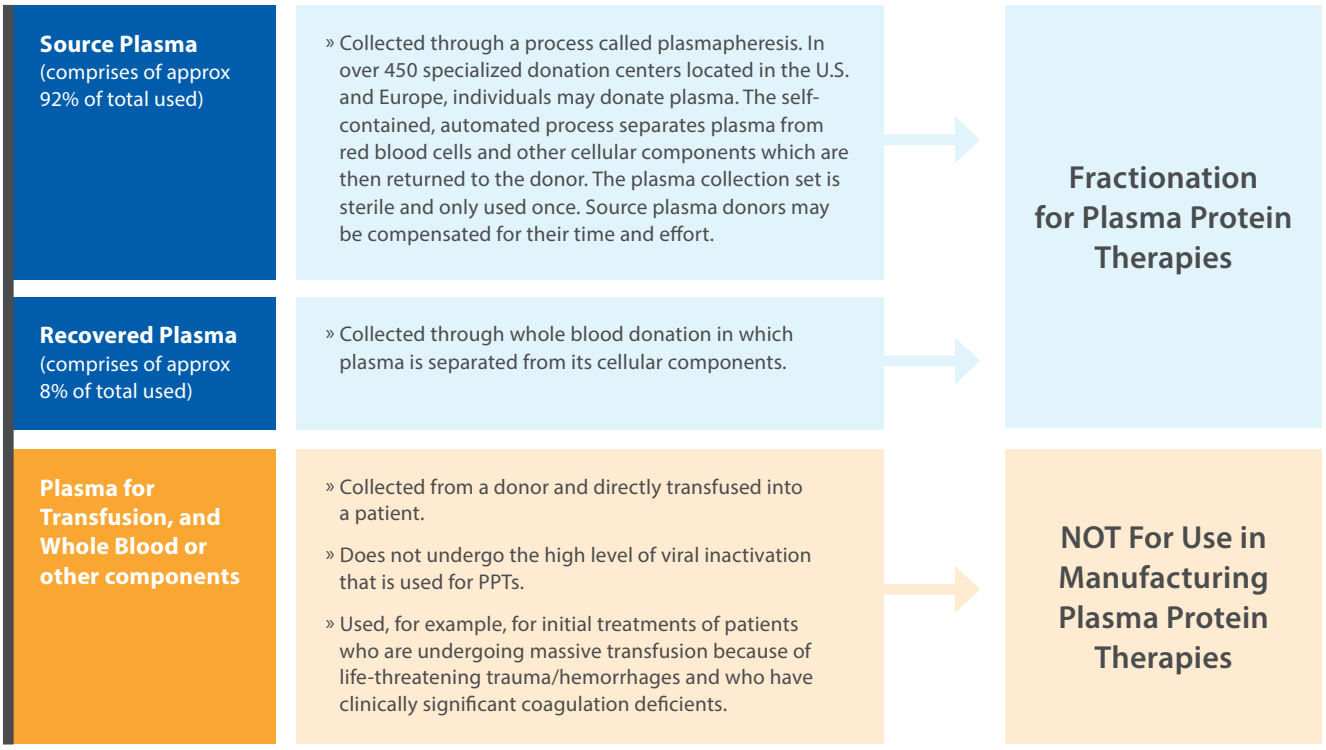
- **Source Plasma:** About 92%[1] of the plasma used in commercial PPT manufacture is collected through a process called plasmapheresis. This is a self-contained, automated process that separates plasma from red blood cells and other cellular components which are then returned to the donor. The plasma collection set is sterile and only used once. The process can take 1.5 hours but up to 830 ml may be collected from a single donor at a time. Because the donor's red blood cells are returned after the plasma is collected, one individual can safely donate plasma up to twice a week. Source plasma is frozen immediately, or within a maximum one hour of collection. Individuals donate source plasma in over 450 specialized donation centers located in the U.S. and Europe.
- **Recovered Plasma:** Roughly 8%[2] of the plasma used originates from recovered plasma, where whole blood is collected from a donor (red cells are not returned to the donor), and later the plasma is separated from the red blood cells prior to the red blood cells being used for transfusion. Recovered plasma is a by-product of whole blood donation. Because red blood cells are not returned to the body, individuals may safely donate only once every 56 days. At a maximum, only 250 ml of recovered plasma can be collected from one donation at a time.

See *Figure 1* (pg.16) for a depiction of the uses of plasma/blood products for patient treatment.

Plasma for Transfusion

Apart from source and recovered plasma, plasma is also collected from a donor and directly transfused into a patient. This plasma, like source and recovered plasma is lifesaving. This plasma is not pooled with donations from other donors and does not undergo the high level of viral inactivation that is used for PPTs. This plasma is not processed for manufacture, or filtered to gain certain protein concentrations. This plasma is often used in trauma cases to replace lost whole blood volume, or it is used as a significantly less effective alternative for patients who desperately need but do not have access to manufactured PPTs.

FIGURE 1
Uses of Plasma/Blood for Patient Treatment



PLASMA FOR COMMERCIAL MANUFACTURE OF PPTs IS SAFE

Safe, quality plasma is the first step in the manufacturing chain for PPTs. Plasma used for PPTs is safe. It is collected from healthy donors using proven, state-of-the-art techniques, and it is collected in accordance with strict ethical principles.

There has not been an incident of transfusion-transmitted infection (i.e., HIV or hepatitis B or C) from commercially-made PPTs in over twenty years. Safety and quality of PPTs is the top priority of the plasma protein therapeutics industry. Both collectors and manufacturers adhere to strict regulatory policies and have instituted Good Manufacturing and Quality Management Practices in every step of plasma collection and manufacturing processes. For source plasma, PPTA-certified collection centers have adopted voluntary standards and other criteria. These robust programs showcase the industry's commitment to continuous improvement and help to ensure the availability of effective and high-quality PPTs. Combined, they put quality and safety in the forefront for patients worldwide.

Source plasma collection centers are certified by the International Quality Plasma Program (IQPP), a rigorous, voluntary program that goes beyond regulatory requirements to further improve the quality of source plasma used for fractionation. IQPP provides independent, third-party evaluation and recognition of a center's adherence to global industry standards for source plasma. The IQPP standards are developed through a transparent process, and are voluntarily adopted by source plasma collection centers. The standards include the following requirements:

- **Community-based Donor:** Requires that donors reside permanently within the defined Donor Recruitment Area of the plasma center. Helps to maintain a steady and reliable donor population and supply of quality plasma.
- **Donor Education:** Requires new donors to engage in an educational program and follow-up assessment regarding HIV/AIDS and activities that place them at risk for HIV/AIDS. Those potential donors who acknowledge being involved in defined high-risk behaviors, are deferred from donating.

- **National Donor Deferral Registry:** Helps ensure that donors deferred for reactive test results do not donate in other facilities. Any individual who tests reactive for HIV, HBV or HCV must be entered into a national database (the National Donor Deferral Registry) used by all IQPP-certified centers in the U.S. All individuals presenting themselves for the first time are checked against the NDDR. Those who have previously been deferred for reactive test results at any participating facility can quickly be identified and rejected utilizing this computerized database.
- **Qualified Donor:** Potential donors must pass two separate medical screenings and testing for HIV, HBV and HCV on two different occasions. Only after satisfactory screenings and negative test results does that person become a Qualified Donor. If a donor does not return within six months, that person loses his/her Qualified Donor status and must qualify again. This standard means that plasma from a one-time-only donor (even when all test results are negative) cannot be used for further manufacture. The standard results in committed donors and eliminates the risk that so-called "test-seekers" are accepted.
- **Viral Marker Standard:** It is important that donations are collected from a low-risk donor population. This standard focuses on that element. Each center is obliged to report its viral marker rates for HIV, HBV and HCV in the donor population. The center's rates are compared to the industry average. Alert limits are set to take into account the number of annual donations. If a center exceeds the limit for any of these viruses or the aggregate of the three viruses, the center will implement corrective actions that will bring the center into compliance with the standard.
- **QSEAL:** Industry also has a voluntary standards program, QSEAL, which complements the IQPP collection standards and addresses manufacture of PPTs. Before manufacture, source plasma used by QSEAL-certified companies is required to be held in inventory for at least sixty days. This gives added protection allowing for destruction of donations that are discovered to be unsuitable after donation. QSEAL standards also contain requirements for viral marker testing of pools at the first homogenous pool, and requirements for intermediate products.

Source plasma collection centers are certified by the International Quality Plasma Program (IQPP), a rigorous, voluntary program that goes beyond regulatory requirements to further improve the quality of source plasma used for fractionation.

INTERNATIONAL QUALITY PLASMA PROGRAM

PLASMA IS COLLECTED UNDER ETHICAL CONDITIONS FROM EDUCATED DONORS

Millions of individuals donate source plasma every year. Donors must be consenting adults. Commercial collection centers are clean, modern facilities that utilize state-of the-art equipment. Voluntary industry-driven collection standards for source plasma centers include many requirements for promotion of donor well-being, health and safety. The standards require centers to maintain a donor educational program that encourages individuals to lead a healthy lifestyle. Another standard contains stipulations to prevent individuals from donating more often than is safe. Industry will also soon publish new specifications for monitoring donor adverse events. The standards even address donor comfort, such as a requirement for ambient temperature of plasma centers. •

SONIA BALBONI, *PPTA Senior Manager, Source & Standards*

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Respect for Autonomy and Donor Compensation

BY JAMES STACEY TAYLOR, Ph.D.

In contemporary bioethics the value of personal autonomy—the capacity of persons to guide and direct their actions and lives in accordance with their own desires and values, rather than to have their decisions made for them by others—reigns supreme.

Healthcare professionals are enjoined to secure their patients' informed consent to the medical procedures that they undergo, and are cautioned against paternalistically imposing their values upon their patients. This concern with the value of personal autonomy is also manifest in discussions of healthcare policy. One of the standard objections to many public health initiatives is that they are paternalistic: that legislators are substituting their judgments concerning health for those of the citizens they are supposed to serve.

Given this contemporary focus in healthcare on the value of personal autonomy recent criticism of offering compensation to plasma donors is nothing less than shocking. The 2013 publication, "Towards Self-sufficiency in Safe Blood and Blood Products based on Voluntary Non-Remunerated Donation, does not mention personal autonomy *at all*—an omission that bodes ill for this document's concern for the rights of individual donors and patients. Similarly, the recent moves in Ontario, Canada, to prohibit compensating plasma donors exhibit a cavalier disregard for the rights of autonomous persons to be free from unnecessary coercive interference.

THE ETHICAL VALUE OF RESPECTING AUTONOMY

These moves away from a focus on respecting patient autonomy are extremely worrying. The current bioethical emphasis on autonomy stems from a recognition that enabling persons to make their own informed healthcare decisions is likely to lead them to make decisions that fit best with their own desires and values. After all, it is likely that the best judge of what is in a person's best interests is the person herself, rather than a third party. (This is not always the case. But a concern for autonomy does not preclude a person from autonomously choosing to seek advice from those who know him well, nor does it preclude a healthcare professional from offering advice, once she has established that it would be welcome.) If we are concerned with human well-being, then, we should respect a person's autonomous decisions rather than impose our views upon her. But the ethical impetus to respect personal autonomy is based on more than just the view that a person's exercise of her autonomy would be instrumentally valuable in securing her well-being. When we respect a person's autonomy we respect her as a being whose interests matter just because she is a self-aware, self-governing, rational agent. We hold her accountable for her actions such that we believe that she could be expected to justify them if she were called upon to do so. In this way, to respect a person's autonomy is to respect her as a member of the moral community. It is to respect her as a person, a being whose decisions are worthy of respect. By contrast, if we fail to respect a person's autonomous decisions we would treat her as being less than a person. We would treat her as we would a small child or an animal; a being whose justifications for her own decisions are not those that we need to take seriously and that we can ignore or override if we see fit to do so. To adopt such an attitude towards a rational adult human is the hallmark of moral arrogance. It is a failure to recognize her as a moral equal—a failure that itself is a serious moral lapse.

AUTONOMY AND COMPENSATED DONATION

But what does this discussion of the ethical requirement to respect autonomy have to do with compensated donation? The answer is simple. While respect for autonomy does not mandate offering compensation to plasma donors—there is obviously nothing unethical about requesting that persons donate plasma without compensation—it does require that persons not be *prohibited* from offering compensation to donors. To prohibit the offer of compensation is to fail to respect the autonomy of the persons offering compensation, the donors to whom this is offered—and the patients who would receive the plasma products that would be produced. When an action is prohibited the persons who are prohibiting it threaten those who would perform it with a penalty if they do so. Those who comply with such prohibitions because they do not wish to incur the threatened penalty are coerced into compliance. And to subject another person to coercion so that she complies with your values rather than acts of hers is the paradigmatic case of failing to respect her autonomy, of failing to allow her to guide her own actions in accordance with her own desires and values free from interference by another. To prohibit offering compensation to donors is thus to fail to respect the autonomy both of those who would otherwise offer such compensation and the would-be donors who would have accepted it. Moreover, prohibiting donor compensation also evinces a failure to respect *patient* autonomy. As well as failing to respect a person's autonomy through coercing her into complying with one's wishes one can also fail to respect it through failing to give her needs and desires due weight in one's deliberations. Since prohibiting donor compensation may lead to a decrease in plasma being available for medical use, any move toward this will evince a failure to respect the autonomy of those patients whose health and lives depend on plasma-based products. Given the necessity of donor compensation to secure an adequate supply of plasma, to argue against donor compensation is to fail to place appropriate moral weight on the needs and desires of patients to secure the treatments that they need. Thus, if one takes patient autonomy as seriously as one should, to advocate policies that would limit the supply of plasma is unethical.

The current bioethical emphasis on autonomy stems from a recognition that enabling persons to make their own informed healthcare decisions is likely to lead them to make decisions that fit best with their own desires and values.

DON'T REGRESS TO A LESS PATIENT-CENTERED AGE

The publication, "Towards Self-sufficiency in Safe Blood and Blood Products based on Voluntary Non-Remunerated Donation," and the recent movement in Ontario to prohibit compensating plasma donors evinces a worrying and unethical interest in turning back the clock to a less patient-centered age. This regressive move should be resisted both by all who recognize the value of personal autonomy, and by all who are concerned with the health and well-being of the patients who depend on the many medical products that are derived from plasma secured through compensated donation. •

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The Effects of Compensating Donations: Time for a Fresh Look

BY NICOLA LACETERA, Ph.D. AND MARIO MACIS, Ph.D.

Most countries around the world forbid monetary compensation to blood and plasma donors. Three main reasons are typically given to justify the prohibition:

1. Monetary rewards might "crowd out" the intrinsic motivation of those individuals who donate in the absence of incentives, thus potentially leading to a reduction in donation rather than an increase;
2. There is a concern that compensation will attract undesirable donors with higher likelihood to carry transmissible diseases;
3. Finally, there is an ethical opposition to monetary compensation for body parts out of concerns of exploitation of the poor, coercion, or repugnance related to commodification of the human body.

These arguments featured prominently in Richard Titmuss's 1971 book, *The Gift Relationship*, which played a very important role both in shaping the public perception about paid blood in particular, and influenced policies that restricted or prohibited compensation to blood donors. For a long time, people simply assumed that Titmuss's arguments were supported by empirical evidence. In fact, at the time of publication of *The Gift Relationship*, and for a few more years thereafter, the available evidence in support of those hypotheses was weak at best. It was almost exclusively based on uncontrolled retrospective studies, surveys, and lab experiments indicating a generalized aversion to rewards. In the last decade, however, several studies have d the

effect of incentives in the field using state-of-the-art empirical methods (e.g., randomized controlled trials) that allow for the measurement of causal effects (as separated from confounding factors). These studies revealed that, contrary to the previous evidence and to common belief, appropriately designed economic incentives can actually increase blood donations without negative consequences on the quality of the blood collected; importantly, the findings are consistent across different types of incentives and different contexts. Thus revealed preferences (i.e. actual behaviors as opposed to stated beliefs relative to hypothetical scenarios) indicate that blood donors respond positively to incentives.

If incentives work, why is there so much opposition to introducing compensation in contexts where it is currently prohibited? And why are some administrations, such as some provinces in Canada, considering a ban on compensating plasma donors?

We believe that, at least in part, these positions are due to a lack of information among the public about the effects of incentives. Make no mistake: collecting useful data and devising solid research designs is not easy, and it was even more difficult before the last couple of decades. This is evidenced especially in the case of plasma donations, for which, to our knowledge, there are no randomized controlled studies that have looked at the effects of offering compensation.

What would be interesting questions to ask here, and consequently, what data would one need and how shall one go to them? For example, an interesting study to conduct would be to look at the effects of setting up a new plasma center in a city or in a neighborhood where none was present before. Questions would include whether people in the area start donating plasma, and what kind of individuals would be attracted (especially in relation to their likelihood to carry diseases or have at-risk behaviors).

Another study may emerge from a policy experiment where, for example, monetary compensation is allowed in certain areas or specific centers, and not in others: Will these different institutional arrangements attract different numbers and "types" of individuals? Such studies (and others) would provide information, for example, about the safety effects of allowing compensation, an issue, of course, of paramount relevance to citizens and policymakers.

A further element of profound difference in thinking about these issues relative to the way that was originally presented in Titmuss's book is that testing and screening technologies have improved dramatically since 1971. This aspect is often overlooked in public debates. A third key departure from the old view of this problem should be to see the questions in dynamic terms and not as a one-shot scenario. Titmuss's analysis, in particular, did not consider that the composition

If incentives work, why is there so much opposition to introducing compensation in contexts where it is currently prohibited? And why are some administrations, such as some provinces in Canada, considering a ban on compensating plasma donors?

of the pool of donors can change over time as a result of screening. Indeed we might expect that when incentives are first introduced, both safe and unsafe donors would be attracted by them, perhaps with a higher-than-average proportion of unsafe donors. However, the unsafe donors would be screened out (and this would happen quickly, we imagine, thanks to modern screening technologies), and only the safe donors will be allowed to donate again in the plasma center. Thus, relatively quickly a center will rely on a pool of healthy, safe donors. Moreover, the presence of an economic reward coupled with the ability of a plasma center to promptly detect unsafe plasma and exclude a person from donating in the future, would actually motivate eligible donors to remain healthy in order not to lose the reward. Thus, in a dynamic perspective, incentives can potentially have a positive effect on the health of the donors, and thus on the safety of the plasma supply.

Now, if we were to rely only on the theoretical considerations just made, as sound as they might seem, we would incur in the same flaw as the old analyses; properly designed empirical interventions of the type described above will need to follow. We believe that the public would benefit greatly from a study that tested these ideas in the field, in a rigorous way.

Another concern of those who oppose compensation to plasma donors is that it would cause people who are currently blood donors to switch to giving plasma. This might or might not be true in reality. We suspect that blood donors and plasma donors are different types of individuals, with different motivations and different socio-economic characteristics such that giving blood and plasma are not perfect substitutes, so we conjecture that the opening of a new plasma center will not steal donors away from not-for-profit blood banks. But again, this is just our hypothesis. With sound empirical evidence available, citizens and policy-makers will be able to make better-informed decisions. •

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Addressing the Questions OF RESIDUAL RISK

BY GEORGE SCHREIBER, SC.D.

The concept of Residual Risk (RR) for plasma donations was discussed in the Winter 2012 issue of *Source*[1]. However, Residual Risk has different interpretations when applied to blood donations vs. plasma donations and there have been questions on its meaning. Here we address the questions but refer the reader to the 2012 article for discussion of the methodology.

Basically RR is just what the name implies; left over risk after all health and test screening and other safety steps are taken. We know that donor health and laboratory screening do not interdict all donors with risk, however. In spite of the high levels of sensitivity in methods used for screening blood and plasma, false negative results may occur because screening tests are unable to detect the infection until a donor's blood or plasma reaches a certain level of analyte detectability. This period between infectiousness and detection is referred to as the infectious window period. The presence of certain viruses in asymptomatic donors who are negative on the screening tests (window period donations) constitutes the major risk of transmission of viruses in blood and plasma products. The RR is then the chance or probability of having a window period infection.

Residual Risk is a useful measure for evaluating safety, assessing changes in the donor base and for generally monitoring performance over time[2,3,4]. There are different applications for residual risk assessment. It is applied by The European Medicines Agency (EMA) to assess the quality of the donor base from which blood or plasma donors are drawn[5]. For PPTA RR is used as a metric to track industry viral risks and assess the probability of possibly infectious donations (window period) entering the manufacturing pool after the application of the 60-day hold period. For blood and blood products RR is the transfusion risk of a recipient receiving an infectious donation. Unlike plasma protein therapeutics, blood products generally are not subject to viral inactivation and removal so the risk is from window period donations that are directly transfused.

Source readers are well aware of the multiple safety measures the plasma industry requires under the PPTA International Quality Plasma Program (IQPP) and the Quality Standards for Excellence, Assurance and Leadership (QSEAL). Two components of these are important in discussing residual risk when applied to plasma donations: the Qualified Donor standard and the Inventory Hold standard. The Qualified Donor standard requires that a donor successfully pass two separate screenings, including infectious disease testing, to be accepted as a plasma donor. It is well known that first time donors have both higher infectious disease prevalence and incidence rates. Thus, only source plasma from Qualified Donors is used for fractionation, minimizing the risk of a window period unit. In 1996, the plasma protein industry instituted a 60-day hold policy whereby all source plasma units are held for a period of 60 days after collection during which any additional information received such as test results and post-donation information can be considered prior to release of the unit for manufacturing. The hold period has proven to be effective in interdicting potentially infectious units and has greatly reduced the residual risk of an infected unit entering the manufacturing pool.

The EMA in their "Guidance on epidemiological data on blood transmissible infections[4]" requests Plasma Master File holders to estimate "the risk of infectious donations of repeat tested donors passing through routine testing, due to collection of donations that are truly negative to the tests in use." These are the window period donations. This calculation, however, differs considerably from the source plasma risk estimate since it discounts the hold period and includes as repeat donors a proportion of donors who would not be Qualified. The EMA RR represents the risk that a repeat seroconverting donor gave a non-detectable infectious unit during the window period and will be higher than our estimate of the probability of an infectious unit being released for manufacturing. EMA acknowledges the industry source plasma risk reduction steps and for submissions under the Guideline request that their benefit be presented in terms of the overall safety strategy. However, the risk estimates are not comparable since the PPTA RR is donation based and only considers Qualified Donations while the EMA RR is donor based and includes all return donors[5]. Return donors include Qualified Donors along with those who make a second Applicant Donation and all lapsed Qualified Donors who have decided to donate again after at least a 180 day lapse in donating. These donors carry higher risk of being window period. Thus the EMA risk calculation does not reflect actual risk of donations that are used for manufacturing.

To put this risk in some fantasy life context, as pointed out in the prior *Source* article; the chance of being killed by an asteroid impact in a lifetime is about the same magnitude as having an infectious unit released for manufacturing.

How are we doing in ensuring high quality donors? *Figure 1* shows the Residual Risk for HIV and HCV for the U.S. source plasma collections for 2001-2012. The low and decreasing risk of a potentially infectious unit being release for manufacturing is currently less than 1 per million donations for HIV and about 1.5 per million for HCV. From 2001-2012 the rates have decreased 36% and 57% for HIV and HCV respectively. Similarly, the decrease in the RR is even more dramatic for HBV (*Figure 2*) 70%. The RR for HBV is higher due to the substantially longer window period. These risks are for potentially infectious donations entering the plasma fractionation pool but it needs to be emphasized that they are window period donations and thus below the level of analytical detection and thus have very low viral loads.

It is important to note is that the risk estimates do not represent the risks after fractionation for the finished product. Fractionation essentially removes or inactivates the three viruses and reduces the risk of viral transmission essentially to zero for the end product.

The low risk reflects the impact of measures industry has taken to maximize plasma safety. This low risk coupled with the critical and highly effective removal and viral inactivation ensure the safety of plasma protein therapeutic products.

The risks of an infectious unit being released for manufacturing are rare. To put this risk in some fantasy life context, as pointed out in the prior Source article; the chance of being killed by an asteroid impact in a lifetime is about the same magnitude as having an infectious unit released for

FIGURE 1
HIV and HCV Residual Risk

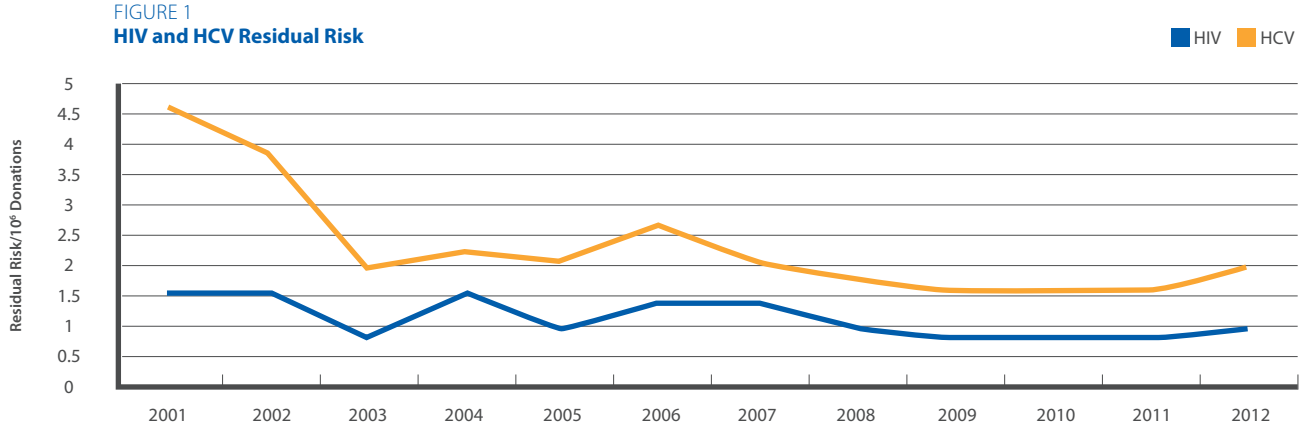
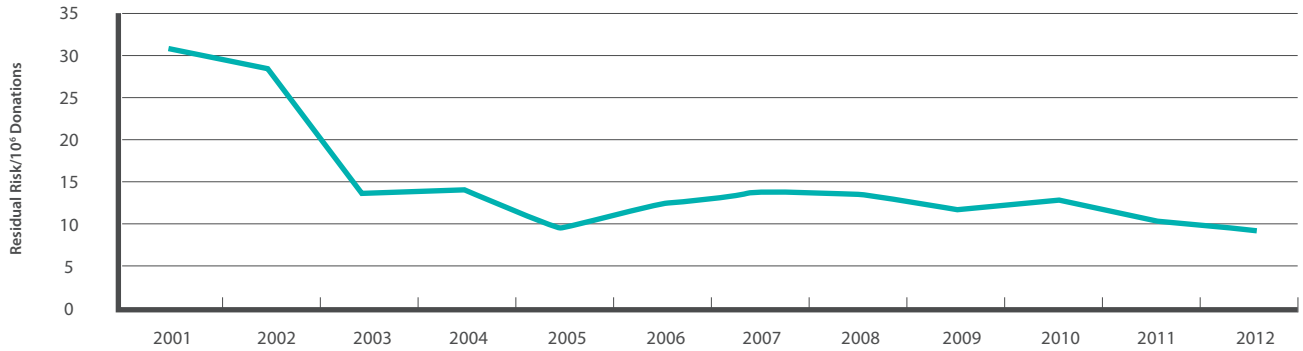


FIGURE 2
HBV Residual Risk



manufacturing. The low residual risk reflects the impact of measures industry has taken to maximize plasma safety. This low risk coupled with the critical and highly effective removal and viral inactivation ensure the safety of plasma protein therapeutic products. Industry's monitoring of Residual Risk of viral infection is an important quality control measure. Deviations from the trends can be detected and if required mitigating strategies considered. A perfect example is the case of HCV where U.S. incidence rates have shown an increase from 2010-2012[6]. We can track industry data to see if this translates into increases in the residual risk estimates for source plasma. As seen in *Figure 1*, an increase in residual risk of about 25% has been observed for the same period. This is substantially less than the increase seen in population incidence rates, but indicates the need to carefully monitor risk trends.

Risk analysis is a valuable tool in the armamentarium of the plasma industry to help ensure that patients are protected against transmission of viral infection from their plasma derived therapies. Transparency in disseminating monitoring data allows patient groups and regulators to evaluate changes in risk in the donor population. •

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The World Health Organization (WHO)

BY JEAN EMMANUEL, M.D.

This is brief summary and overview of the important and vital role of the largest United Nations Organisation, which is mandated to be responsible for global health issues and falls far short of covering all the activities and achievements of this much respected organization; the dedication of its members, staff, collaborating partners, expert advisers and supporting organizations.

The information for the narrative has been taken from the sources, as detailed in the references and from personal experience working for WHO in Geneva, and on which the writer was heavily reliant.

In all instances of attempting to describe and explain the complex nature of such a prestigious and important international organization, within a limited narrative, there will be details and information, which will be incomplete and which may be considered of importance, but not included, for which the writer is personally responsible and regrets.

HISTORY

At the end of World War II, in 1945, a proposal was placed before the United Nations Conference on International Organizations, held in San Francisco California, by Brazil and China, on the need to establish an autonomous health organization, within the United Nations System. The proposal was unanimously approved and in 1946, an Interim Committee was appointed and the Constitution of the World Health Organization (WHO) was approved.

On 7th April 1948, WHO officially came into being, which day is annually celebrated as World Health Day and to mark the importance of the occasion each year, a Health Theme, judged to be of global significance, is chosen.

WHO has, since its inception, fostered and led global collaboration and co-operation in all areas of health, at global, regional and national level. Through WHO leadership and global coordination efforts major health milestones have been successfully achieved. Eradication of deadly diseases, such as Small Pox, was achieved, between 1967 and 1979, saving many millions of US dollars in health care costs, but most importantly, saving many millions of lives from death or severe disfigurement, and this across all economic boundaries, rich and poor nations alike, bringing the dream of Health for all within reach.

STRUCTURE

WHO's Constitution defines its role as one of being the directing and coordinating authority on international health work, which aim is "the attainment by all peoples of the highest possible level of health"; [defined as - "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."(sic)]

WHO determines priority areas of work, broadly based on the seven specifically agreed number of responsibilities, which include:

1. Stimulating the eradication of epidemic, endemic and other diseases;
2. Promoting improved nutrition, housing, sanitation, working conditions and other aspects of environment hygiene;
3. Fostering cooperation among scientific and professional groups, which contribute to the advancement of health;
4. Proposing international conventions and agreements in health matters;
5. Promoting and conducting research in the field of health;
6. Developing international standards for food, biological and pharmaceutical products; and
7. Assisting in developing an informed public opinion among all peoples on matters of health.

WHO is, by necessity, a bureaucratic organization, led by a Director General (DG) appointed for a term of 5 years, by the World Health Assembly (WHA) on nomination by the Executive Board (EB). Regional Directors are appointed by the EB in agreement with respective Regional Committees. The WHO DG appoints personnel in WHO headquarters (HQ), Geneva in accordance with staff regulations, which have been established by the WHA. Staff at regional level are appointed by each respective Regional Director.

WHO is a "Specialised Agency" as provided for in the Charter of the United Nations with reciprocity between the two organizations, governed by a formal agreement on the exchange of information and exchange of ideas.

WHO has its own governing body, membership and budget. The largest contribution is assessed one quarter of WHO's budget, while the smaller contributing countries are expected to pay one hundredth of the WHO Budget.

Regardless of the amount of the contribution, each member has one vote.

WHO's programme budget is prepared in 2 year cycles in accordance with the General Programme of Work agreed plan for a specific period [six years], with reference to the overall policies and principles approved by WHA.

In addition to the regular budget, which is provided by WHO Member States, voluntary contributions are made by funding agencies, countries and benefactors, to meet financial requirements in specific projects, disaster relief, natural catastrophes, medical research, disease eradication projects [polio; measles, leprosy, malaria, HIV] and selected priority areas of work. WHO also coordinates and advocates for funding of health related development projects through bilateral and multi-bilateral funding sources, where projects funds are channelled through WHO sub accounts, usually a programme support cost (PSC) is levied for the management and administration of the funds.

WHO is comprised of three constituted bodies: the WHA, which meets annually in May in Geneva Switzerland; the EB; and the WHO Secretariat. WHA Meetings are attended by delegations from the member states and representatives from other international bodies and nongovernmental organizations (NGOs), whose main tasks are to approve the biennial budget and decide on main policy issues.

The EB comprises 31 members, who are technically qualified in the field of Health and each appointed by designated WHO Member States elected by WHA. The Executive Board usually meets twice annually, the main meeting being January and then a short meeting following each WHA in May. The EB functions as the executive branch of the WHA, preparing the agenda for each session of WHA and submits to WHA the General Programme of Work. EB acts on behalf of the whole WHO membership.

FUNCTION

The work of WHO is carried out by a secretariat of technical, administrative and support staff in the Geneva WHO, with the DG as the technical and administrative head. WHO HQ, regional offices and country WHO staff, are made up of professionals, who are recruited for their skills, experience and expertise in accordance with WHO Staff Regulations, for which the selection is regionally representative of WHO Member States.

WHA Resolutions are tabled, discussed and adopted by Ministers of Health for enactment, in accordance with the programme of work, at the meetings of the WHA in May.

In addition to the important annual WHA Meetings in Geneva, WHO, at the request of the United Nations (UN) General Assembly, takes part in important Conferences on Global Issues; through WHO Regional Offices WHO takes part in and establishes collaboration with key regional bodies and plays an important role influencing policies and issues of economic importance for health; safety and human rights. WHO works closely with other UN Bodies to improve collaboration in the provision of health care, disease prevention and in meeting goals relating to WHA Resolutions.

WHO staff members are selected from scientists, medical health workers and other experts in the specific areas of WHO's responsibility, with support staff for the organisations effective organisation and management. WHO has its HQ in Geneva, Switzerland and has 6 Regional Offices; WHO Regional Office for the Americas (AMRO), in Washington, DC, USA, which joined with the previously established Pan American Sanitary Bureau (PAHO), in Washington, DC, USA; WHO Regional Office for Europe (EURO), in Copenhagen, Denmark; WHO Regional Office for the Eastern Mediterranean (EMRO) in Cairo, Egypt, [representing the North African and Arab States]; WHO Regional

The decisions and recommendation of the Committee are based entirely on scientific principles and considerations of public health.

Office for Africa (AFRO) in Brazzaville Congo; WHO Regional Office for South-East Asia (SEARO) in Delhi India; and the WHO Regional Office for the Western Pacific (WPRO); which offices were established to meet operational and geopolitical expectations. In 2 cases, countries have been assigned to Regional Offices outside the expected natural geographical boundaries, in order avoid any possible political differences and conflicts in Regional Meetings; Notably North Korea sits, not with South Korea, in the Western Pacific Regional Office (WPRO), but in SEARO and Israel sits not in EMRO but in EURO. There is also the WHO Liaison Office with the UN United Nations Plaza, New York NY USA.

Regional Directors participate in selected EB meetings and in all WHA annual meetings, providing support and assistance to their respective Ministers of Health from their region.

In nearly every country there is a WHO Country Office, especially in the developing countries, which office is led by a resident World Health Representative (WR), who liaises and works with the National Health Authority, responsible for WHO activities and supports in the planning and management of national health policies, identifying extra budgetary funding needs and possible donor sources to meet implementation of important health related programmes.

WHO has 6 approved official languages, English and French; and also Arabic, Chinese, Spanish and Russian, which languages have the benefit of simultaneous translation during the WHA Meetings and other selected meetings relating to their level and importance and composition of the invited participants.

The work of WHO would not be possible, without the cooperation and agreement of National Health Authorities, many of which have the expertise and infrastructure to assist WHO to carry out research, coordinate information, seek solutions and propose actions to identify re-emerging old diseases and identify new diseases and infectious agents by establishing global networks for information gathering through meetings convened by WHO of expert advisory panel members and other international and regional experts, all of which result in formulating appropriate responses at national, regional and global level.

WHO has identified a selected and specifically chosen a number of Centres of Excellence and designated them as WHO Collaborating and Reference Centres.

There are more than 1,200 WHO Collaborating Centres globally. These academic and medical centres are funded by national governments, however, they contribute to WHO's research agenda and program priorities.

These centres form a collaborative global network on surveillance and serve as custodians of WHO's Global Reference Standards and Master Files. They provide services in many areas such as External Quality Assessment Schemes (EQAS) to assist country and regional programmes, which provides continuing medical education and training support, research and training, raising the health care and development at national, regional and global level. Advisory Committees of international and Regional Experts have been established, which assist and provide WHO in meeting its agreed objectives in responding to health issues in all its stated priority areas, especial in setting and maintaining standards.

WHO recognises specifically selected Governmental and NGOs, as well as Societies and Associations, representing Health Professionals and Patient Groups, which can, and do, assist WHO in its work and appoints these as Organizations in Official relations with WHO. These Organizations and bodies bring information and assistance to the work of WHO through their membership relevant to WHO's area of work and are able to table agenda items for consideration and discussion at WHA Meetings, for the attention of the gathering of Ministers of Health from WHO Member States.

"The WHO Expert Committee on Biological Standardization (ECBS) was established in 1947 to provide detailed recommendations and guidelines for the manufacturing, licensing and control of blood products and related in vitro diagnostic tests, biotechnology products and vaccines along with the establishment of WHO Biological Reference Materials. The ECBS meets on an annual basis and reports directly to the EB.

Members of the Expert Committee are scientists from National Regulatory Agencies, academia, research institutes and public health bodies. The decisions and recommendation of the Committee are based entirely on scientific principles and considerations of public health.

Written guidelines and recommendations submitted to the ECBS are drafted through a consultative process, during which WHO brings together experts in the topic from around the world. Reference materials are established through scientific studies involving participation of a large number of laboratories worldwide. The proceedings of the meetings of the ECBS are published in the WHO Technical Report Series (TRS). They provide the information on the establishment, discontinuation and replacement of the WHO Biological Reference Materials as well as on the adoption of Guidelines and Recommendations." •

JEAN EMMANUEL, M.D.

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Procleix NAT Solutions

By Hologic and Grifols

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The Story of Ontario:

POLICYMAKING AND MISUNDERSTANDINGS

BY JOSHUA PENROD

Questions on the ethics behind compensating plasma donors are as old as the practice itself. For the past decade the issue has clouded policy debates, particularly in Europe. But in 2014, the ragged edge of the discussion involving the appropriateness of a policy supporting compensation for donors has drifted outside the context of the European Parliament and the offices of European national policymakers.

In the United States, in 2013, nearly 29,000,000 source plasma donations were given and used around the world, including Canada; but this year in Ontario, the premise of allowing compensated donation on their own turf has come under scrutiny.

The Ontario case has been covered before in *The Source*; there's little need to repeat those events except to say that there was a legislative attempt to ban compensated donation in Ontario. This spring, Parliament dissolved over heated policy issues before hearings could be held. Following Parliamentary elections in June, a new government formed and soon thereafter announced its intent to re-introduce similar legislation aimed to produce a similar result. At the same time, news features and op-eds have run the press circuit.

Various groups may indeed differ on the issue as far as what constitutes an ethical practice, what constitutes safety, and many other concerns and problems that span the spectrum of plasma donation. But one characteristic common to the detractors of the practice is a lack of knowledge about plasma donation and why donor compensation has taken root in the US and elsewhere.

For several years now, PPTA and member companies have engaged in a public awareness campaign in an effort to dispel myths about the plasma collection process. This includes promulgating messages about the vital uses of plasma, how plasma is collected, how patients benefit from plasma, testing, quality, and safety, and why we compensate donors. The last question can be both simple and complex: plasmapheresis is a time-consuming process and the industry requires many donations in order to make finished plasma therapies. Also, it includes recognition of a regular donor's time and commitment to the process and allows reciprocity in the relationship.

The Ontario situation, in particular, has become a microcosm of the ongoing controversy and misunderstandings about plasma and plasma products. Many parties have expressed concern about safety, the meaning of compensation, how donors are treated, and what sort of people the donors are.

The questions stem from an historical image of the industry which has now become embedded as a stereotype of the plasma center and the plasma donor himself. The stereotype has its roots in the hypothetical "donor profiles" imagined by Richard Titmuss in his 1971 book, The Gift Relationship, wherein, without empirical data, plasma donors were boxed into the category of "paid donor." The stereotype has persisted for more than 40 years.

An offshoot of the cultural stereotype depicting donors, are concerns about safety. The discussion takes two major forms: the safety of the plasma itself, and the safety of the individual giving the donation. Ultimately, the layers of quality and safety put in place by industry provide further assurance of a donation process that is already proven safe. Testing, donor assessment and screening, and a fully integrated process for donors and donor management are an irreplaceable part of contemporary plasma donation. Because of current industry safeguards and practices, any argument that compensation leads to unsafe product is outdated. In fact, Canadian policymakers have stated that national concerns have nothing to do with plasma safety; they agree that products made from compensated donors or made in the United States, are safe. Recent quotes by newly-installed Ontario Minister of Health Eric Hoskins underscores this.

Rather than donor safety, the present Canadian argument seems to be that compensation is inherently unethical, and therefore, even if the fruits of compensation undertaken in other jurisdictions may be reaped in Canada, the practice of compensation in Canada should not be allowed. In other words, they seem to argue that Canadians may become tainted by donating plasma for compensation, although the plasma itself would still be unsullied. This position is such that any monetary value ascribed to any part of the human body stems from wrong assumptions about the nature of economics and demonstrates a lack of affinity for pro-social policy objectives. The argument relies on a very specific application of the concept, as working people constantly trade their bodies for value, in the sense of labor and salary. The "something different" is constructed as some other ineffable quality relating to the constituents of the body itself, however. The objections can be religious or sprout from other ethical systems in which the social is elevated further, and that the individual's determination of the value of their individual body is deferred in favor of the state's decision. This is typically described in terms of protection from exploitation, wherein an actor which is perceived to possess greater power overrides a lesser-powered party or individual. Oftentimes, this has rational benefit and protects basic freedoms; other times, however, it militates against individual volition and deprives fundamental rights of association and participation.

Interestingly, much of the most balanced and well-informed commentary emerged from the patient communities themselves who have intimate familiarity with plasma therapies and, of course, the serious conditions that are treated by products produced from human plasma. PPTA has also contributed discussion points and items for consideration in the policymaking process, as has Canadian Blood Services. All of these voices have advocated for a balanced and sensible approach which take into account a number of social factors involved. Shortly after several articles and the Ontario Ministry of Health's announcement, one Canadian patient group posted: "Does Anyone Care What Patients Think?"

One of the most pernicious and persistent aspects of the debate is the confusion between blood/plasma for transfusibles use versus plasma collected specifically for further manufacture. Among the foremost making this distinction has been the organization responsible for collection of transfusible components in Ontario: Canadian Blood Services. Time and again, efforts by CBS and others, including PPTA, have been directed toward education highlighting the discrepancy. This remains an important, basic fact that continues to be overlooked.

Differentiation between plasma and blood has long been an objective of the industry, and is often recognized by scientific authorities, both governmental and otherwise, as a path by which the most effective regulations can be promulgated. These outcomes include critical distinctions about policies involving donor deferral, product safety, blood component availability, and many other related items. All too often, however, policymakers are not aware of these important distinctions, and the product is unfortunately cookie-cutter regulations which hinder the availability of safe product. Thus, lumping transfusibles and source plasma products together demonstrates not only a lack of understanding, but a disregard for science and well-settled regulatory policy made by leading scientific bodies around the world.

The issues in Canada are the ingredients for a perfect storm. Most concerning- is that an honorable system created to effect meaningful policy may be subverted. The most adverse consequence is the harm that could be wrought for patients' health and the confidence they have in their medicines. Never before have so many patients been treated by safer and high-quality therapies. Yet, as shown by the Canadian situation, they still face these needless obstacles. Patients deserve better, as do the many millions of donors who have contributed to the availability of life-saving therapies today. •

JOSHUA PENROD, *PPTA Vice President, Source*

CANADIAN BLOOD SERVICES VIEWPOINT

To the editor,

Thank you for your invitation to comment on the recent debate on paying donors for plasma donations in Canada. Your readers may be aware that in July of this year, the Province of Ontario introduced legislation to prohibit the payment of plasma donors. Canadian Blood Services recognizes the right of the Government of Ontario to proceed in this way, and values the government's role in preserving voluntary blood and plasma donation in that province. Given the complexity of this issue and the public debate surrounding it, we feel it important to clarify our organization's viewpoint.
In short, we believe:

- **This is an issue of public policy, not product or patient safety.**
- **Pharmaceuticals made with plasma from paid donors are safe, lifesaving products for patients in Canada and around the world.**
- **Canadian Blood Services remains committed to voluntary donation for its donors.**

Canadian Blood Services provides blood and blood products to all provinces and territories in Canada except Quebec. We manage a national voluntary blood donation system that provides a safe, affordable and accessible supply of blood, blood products and their alternatives to hospitals across the country. All blood components used for transfusion in Canada are donated by volunteer donors, and we are fully committed to a volunteer system for blood donation. The safety of blood components is assured through a rigorous and multi-tiered process that includes donor screening, transmissible disease testing, and product manipulation.

Canadian Blood Services also manages a national bulk purchase and distribution program for plasma protein products. The demand for many of these plasma products in Canada, as in other jurisdictions around the world, continues to increase. For many patients, plasma products are crucial, lifesaving therapies for which there are no alternatives.

To meet the growing need, Canadian Blood Services collects plasma exclusively from volunteer Canadian donors, and sends it to fractionation companies in the United States and Europe that make plasma products. The finished products are returned to Canada for distribution to hospitals. However, the plasma collected in Canada today provides sufficient starting material to meet only about 30 percent of overall patient needs. To meet the total demand, we also purchase plasma products from the international commercial plasma industry, which does pay its donors and has done so for decades.

This is neither new nor unique to Canada. As your readers know well, the majority of the world's supply of plasma products comes from paid donors. Significant improvements to fractionation processes since the 1980s have made plasma products remarkably safe. Manufacturers must meet the stringent quality and safety standards of regulators such as Health Canada and the United States Food and Drug Administration (FDA). As a result, more than 25 years of clinical experience and numerous studies have shown plasma products derived from paid commercial sources are just as safe as products made from volunteer donors. Canadian Blood Services recognizes and accepts this important set of facts.

Canadian Blood Services is committed to a volunteer blood donation system and at the same time acknowledges the importance of paid plasma donations to meet international demand for critical drug therapies. Operating a safe system means not only meeting product quality and safety requirements, but also ensuring security of supply for patients. Thousands of patients depend on lifesaving plasma products, and without those produced using plasma from paid donors, the needs of these patients would not be met nationally or globally.

Sincerely,

Dr. Graham D. Sher, M.D., Ph.D., *Chief Executive Officer*

WHY THEY ARE MADE THIS WAY – Plasma Derivatives

BY DON BAKER, Ph.D.

Among the geeky shows with a target audience of science and engineering nerds, the Science Channel's "How It's Made" is a standout. In continuous production since 2001 this show has produced hundreds of episodes documenting the manufacture of the most humble household appliance (think toilets) to esoteric medical instruments such as MRI scanners. The long running appeal of this show must resonate with the universal human curiosity about how things are put together. In this article I hope to connect to that common interest.

Not exactly with a "How It's Made" perspective on plasma derivatives since readers of this magazine already have at least a general understanding of plasma derivative manufacture but rather an examination of a "Why They are Made this Way". The focus will be on some of the unique factors associated with the production of these therapeutic agents and how these factors shape our approach to modern manufacturing.

As pharmaceutical agents the most unique feature of human plasma derivatives is the obvious. The production raw material is human plasma. To the casual observer, the medical use of whole blood or plasma feels reasonably obvious and natural, remove blood from one individual, transfuse it into another. However the concept that one could take multiple units of plasma, pool them and purify individual plasma components and that the isolated components would have more medical value than the component plasma is not immediately obvious. The fact that plasma derivatives first came into being and perhaps exist at all is arguably an unlikely accident. Their origin arose out of the confluence of medical need in a global conflict, developments in protein biochemistry and the presence of a

Fortunately for humanity and our industry, there was a “black swan” event. Plasma derivatives were developed and these products have provided life sustaining and lifesaving medical benefit to millions.

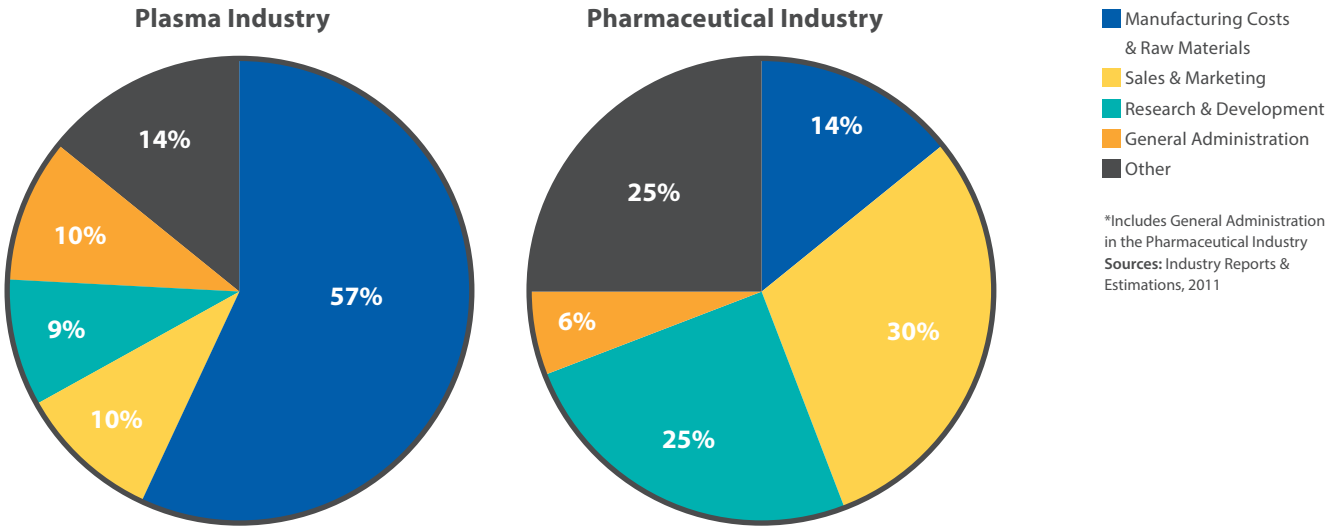
few individuals such as Edwin Cohn who had the knowledge, passion, and influence necessary to provide the leadership for plasma derivative development. To get a flavor of just how improbable these products are, try imagining the challenges one would face today in constructing a business plan for the *de novo* development of these agents. A consideration of the associated legal and liability issues alone would likely doom any funding of plasma derivative development.

Fortunately for humanity and our industry, there was a “black swan” event. Plasma derivatives were developed and these products have provided life sustaining and lifesaving medical benefit to millions. While many factors come into play when companies contemplate the manufacture of any class of therapeutics, for plasma derivatives the complexity that underlies their manufacture is undoubtedly a major deterrent. To illustrate how the complexity of these products impacts manufacturing I will utilize conventional synthetic drugs as a comparator. These products make up the majority of prescription medicines. For these “typical” pharmaceutical products, a production run is initiated with one to a few lots of starting material. Acquisition and release of these raw materials as “suitable for further manufacture” requires qualification of a limited number of suppliers and the performance of small number of incoming release tests. The release testing is often just visual inspection of a container, review of a supplier certificate of analysis, and the performance of a single test to confirm identity. Compare this situation to that which occurs in the production of a single lot of a plasma derivative such as intravenous immunoglobulin (IVIG). A lot size of 50 Kg IVIG requires the collection, testing, and release of approximately 16,000 to 60,000 lots of the raw material, a unit of plasma (the variation is driven by the unit volume of the plasma type, source, ~880 ml, or recovered, ~240 ml, used). Each supplier of the plasma (otherwise known as the donor) must also be individually qualified. Taken together, these activities approximately 200 information inputs per unit, each production run requires generating, evaluating and storing ~3,000,000 to 12,000,000 raw material data points.

Obviously this is a staggering amount of information to manage and preserve . Current Good Manufacturing Procedures (cGMP) for pharmaceuticals require that manufacturers not only perform qualification of the raw materials but also be able to forward and reverse track the raw materials, throughout the production process and ultimately to all recipients. This means that the manufacturers need credible systems which can track forward and back each unit of plasma from the vein of the donor to the vein of all recipients. The data analysis required for a task of this magnitude helps explain why over the preceding decades commercial manufacturers have dramatically increased the size and capabilities of their computerized manufacturing networks. The systems necessary to manage this data intensive environment have significant economies of scale. Simply put, computers scale efficiently, humans don’t. Small scale manufacturers have great difficulty amortizing the cost of automated systems over small production volumes.

Raw material tracking is, of course, far from the only complex and demanding area of plasma derivative manufacture. These therapeutics also have three other general features which tend to differentiate them from traditional pharmaceuticals. The first and most important is the moral/financial penalties associated with raw material loss. Every donation of plasma is voluntary and waste through inefficiency is, simply put, an abuse of the trust donors place in manufacturers. Fundamentally avoidable waste or low yield processes are in a sense unethical. With both

FIGURE 1
Manufacturing Cost Structures of Plasma-based Protein Therapies and of Chemical-based Pharmaceuticals, 2011



under-diagnosis in the developed world and under-treatment in the developing world, there is currently a patient for every product vial produced and inefficiency means some patient unnecessarily is deprived of the benefit of these therapeutics. Fortunately, economic factors reinforce this ethical dimension. Conventional pharmaceuticals typically have a cost structure in which raw materials represent a small percentage of the total cost of manufacture. For simple therapeutic solutions, the raw material cost is often less than the cost of the final product container. For plasma derivatives the situation is quite different, plasma costs account for 57% of the cost of manufacture as pictured. This raw material cost is magnified by the 60 day plasma hold (no just-in-time delivery for plasma) which increases inventory costs. The relatively high raw material costs cascades through the production process in the form of Work-in Progress (WiP) inventory costs. These costs are further amplified by the relatively long, typically months, of production time from plasma collection to final product. In summary, for cost effective production, plasma loss in manufacture must be driven to as low a level as possible.

The second differentiating feature of plasma derivatives is the inherent complexity and mutability of the raw material and intermediates. Plasma is sometimes characterized as a living material. This is, of course, not true however plasma does share some characteristics of living systems. Plasma has a complex composition. Most of the components show biochemical activities and can react with themselves and/or other components. Multiple environmental factors, such as temperature, pH, ionic strength, material surfaces, etc. will cause compositional changes usually in a non-linear fashion (small change big impact). Like a living system, plasma is also extremely sensitive to microbial contamination. All of these features were, of course, well understood by Cohn and coworkers. The success of their foundational work was owed as much too rigorous process control as to scientific expertise.

When dealing with complex systems, there is a truism in manufacturing that complexity is best offset by simplicity. As far as possible, you reduce allowable operating ranges, variations in procedures, process hold times, etc. The intent is to simplify the available options at any step. Obviously this requires substantive expertise and investment in process design and development. Properly implemented, this reduction in variation reproducibly leads to higher yields and improved quality. In short, since you can't change the nature of your starting material, you obtain repeatable results by consistent, strict control of the manufacturing materials, processes, and environment. This stringent management naturally comes with a substantive and continuing investment in staff training, process development, and facilities. Again, operational scale greatly enhances the return on this investment.

The third differentiating factor arises from a combination of the above two. In an environment with significant material and production costs and lengthy production runs, efficient manufacturing requires high facility capacity utilization. Many production areas in plasma derivative manufacturing facilities commonly run at even higher utilization than conventional pharmaceutical manufacturing, where 65% to 75% capacity utilization is the norm. The benefits of very high facility utilization, working your assets hard, while intuitively obvious are not simple to attain. Ideally, your manufacturing facility is optimally designed so that all available production slots are utilized, raw material and WiP inventory is minimized, and production targets are met. The ability to achieve this sweet spot requires a sophisticated management of ancillary manufacturing activities such as production planning, logistics, process monitoring, and maintenance. The necessity for wide ranging capabilities in these areas in turn favors larger production plants. Large organizations can afford to maintain the expertise breadth to provide comprehensive support services in these areas. With high levels of facility utilization, manufacturers also derive substantive immediate benefit from the implementation of new technologies or processes which introduce additional efficiencies. If you are operating at 65% capacity and the introduction of a new technology allows you to provide the same output at 60% facility utilization the advantages of change are limited. In contrast, in a 100% utilization setting, getting 5% more product from the same facility (in an environment where every vial has a customer) provides significant advantage.

In summary, the current realities in the manufacture of plasma derivatives favor large manufacturing networks with plasma throughputs in the millions of liters per year. Operating in competitive markets with professional independent regulation, these large entities produce plasma derivatives with the highest quality and the lowest possible production cost. Despite the organic pressures which favor large production entities with independent oversight, there are those who advocate a national self -sufficiency program in which governmental entities would produce plasma derivatives required for their region.

In the introduction to this report, the authors layout the rationales for their belief in the desirability of self-sufficiency. In this discussion one point which was made that would give rise to little disagreement is the view that "... blood and blood products are a precious national resource that will remain limited by nature." I think this statement would resonate with everyone in our industry. However, from this point of general agreement to the view that national governments are innately blessed with the wisdom to best utilize this resource, is much less likely to evoke universal agreement. The collective human experience is arguably most consistent with the view

In this discussion one point which was made that would give rise to little disagreement is the view that "… blood and blood products are a precious national resource that will remain limited by nature."

that national governments have not demonstrated that are inherently better able than any other entity to sustainably manage any national resource. In fact, a fair reading of history would suggest that the state producers often have the unchecked ability to mismanage a resource while utilizing the considerable power of the state to deflect or discourage criticism. This situation where the state polices itself, often devolves into crony regulation. These factors tend to make a government organization the least fit approach for efficient, sustainable resource utilization. Even assuming that one believed that for plasma derivatives, state manufacturing organizations were philosophically preferable, given that healthcare dollars are globally a scarce and limited resource, this approach to production means that resources will be inefficiently used. With limited available funding, governments will have to short-change patients in one area to support inefficient provision of plasma derived therapeutics in another. Potentially even more problematic for patients, will be that self-sufficiency becomes in practice not what the market needs but what can be produced by a government monopoly in a closed marketplace.

Does this mean that there is no desirable role for the state in plasma derivative production? Certainly activities by countries to encourage blood and plasma donation are of value. Public/private partnerships in which countries enter into relationships with experienced fractionators to produce plasma derivatives (toll fractionation, joint facilities etc.) provide a potentially useful mechanism for expanding plasma derivative supply. So long as markets remain open, and regulation is credibly independent, the provision of sufficient high quality products is supported.

DON BAKER, Ph.D.

Sources:

[1]In this article plasma derivatives will be defined as therapeutic substances derived from plasma and processed so as to provide a defined therapeutic composition.

[2]A black swan event is a high-impact, hard to predict, and rare event that is beyond the realm of normal expectations.

[3]Depending on the country regulatory agencies require that donor information be retained for up to 30 years.

[4]In this discussion the concept of "cost" will be treated somewhat simplistically essentially plasma cost will be considered as the free market spot purchase cost.

[5]World Health Organization.Towards Self-Sufficiency in Safe Blood and Blood Products based on Voluntary Non-Remunerated Donation 2013.

Self-Sufficiency
FACTS AND PITFALLS!

BY PATRICK ROBERT

For a given country or region, there are two ways to achieve self-sufficiency in plasma products procurement, defined as its ability to secure all the therapeutic plasma products it needs from its own plasma supply, regardless of where it is fractionated:

1. To collect enough plasma to meet the demand as determined by patients' needs, or
2. To limit the demand, and generate only the volume plasma required to meet it.

Data collected by the Marketing Research Bureau (MRB) in 15 selected countries show that self-sufficiency levels in the procurement of albumin, plasma-derived factor VIII and intravenous/subcutaneous immune globulin (referred to as "IVIG" in this article) vary significantly from one country to another.

INTRAVENOUS AND SUBCUTANEOUS IMMUNE GLOBULIN (IVIG/SCIG)

Self-Sufficiency as Measured on the Basis of the Existing Unit Sales

Table 1 (pg. 35) shows the consumption of IVIG in 15 countries as reported in the MRB reports (column a), the volume of plasma available for fractionation (recovered and source) (column b), the theoretical production of IVIG based on the volume of plasma available, using a yield of 4 grams per liter (column c), and the self-sufficiency ratio in IVIG procurement (column d) which is the percentage ratio of the data in column (c) over those in column (a).

These ratios are based on the IVIG unit sales in each country. The overall average self-sufficiency ratio of the fifteen countries under review is 137%. This would suggest the existence of an over-supply of plasma when aggregating the data of these countries. However, this figure is misleading: excluding the United States, which supplies the world's largest volume of plasma for fractionation, brings this ratio down to 93%. Excluding the five countries which supply the highest volume of source plasma (Austria, China, Czech Republic, Germany and the United States) brings the ratio down to 57%. This means that these five countries supply enough plasma to produce IVIG for their own domestic requirements as well as for export to other countries, whose domestic plasma supply, mainly recovered plasma, does not suffice to meet the IVIG market needs.

Incidentally, the large quantities of plasma collected in these countries is a consequence of their legislations that allow a higher volume drawn per donor (e.g. twice a week in the U.S.) than in most other countries (twice a month, with an upper limit). Donor compensation is not the primary cause of these large collection volumes, as it is often erroneously believed.

For historical, financial, regulatory and commercial reasons, the average consumption of IVIG/SCIG varies considerably from one country to another, as shown in *Table 2* (pg. 35), which also shows the average consumption for albumin and Factor VIII.

Chart 1 (pg. 38) depicts the average IVIG/SCIG consumption from highest consumption per million people to the lowest.

Self-Sufficiency as Measured on the Basis of a Demand of 60 Kg. per Million People

If the fifteen countries reviewed consumed an average of 60 Kilograms of IVIG per million inhabitants (about the same level as Germany, Italy and Spain) instead of their current demand, their self-sufficiency ratios would differ markedly: China, Russia, Japan, and Brazil, among others, would display lower self-sufficiency levels in IVIG supply than those obtained when applying their current consumption.

Conversely, the few countries which supply comparatively large quantities of plasma for fractionation, mainly of commercial origin (source plasma) would achieve self-sufficiency ratios well above 200% (Austria, Czech Republic, Germany and the United States), allowing them to export IVIG or plasma, as their domestic needs would be amply covered.

The overall average self-sufficiency ratio of the fifteen countries under review is 137%. This would suggest the existence of an over-supply of plasma when aggregating the data of these countries. However, this figure is misleading.

In other words, in *Table 3* (pg. 36), China, Japan, the Czech Republic and Russia show relatively high self-sufficiency ratios for IVIG supply because their consumption per inhabitant is comparatively low. In contrast, if these countries consumed IVIG at levels per capita comparable to those of western European countries, their sufficiency levels for this product would be signficantly lower.

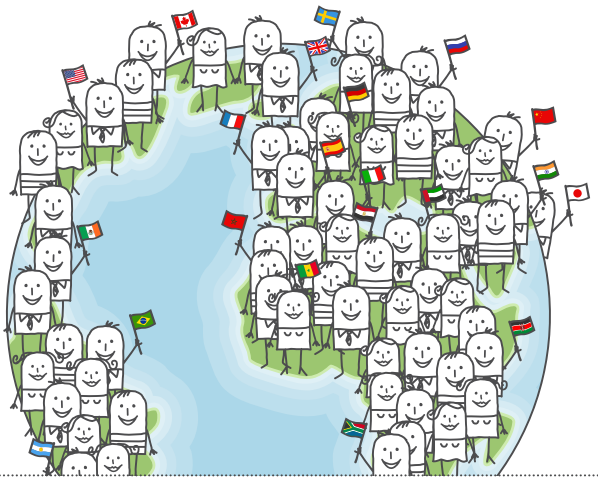
Under this theoretical scenario, the average self-sufficiency ratio of the fifteen countries under review is only 62%, illustrating a need for more plasma in order to achieve an average consumption level of 60 kilograms per million inhabitants in all of them.

Brazil will need to generate or import 8.97 metric tons of IVIG in order to attain a consumption level of 60 Kg. per million inhabitant. At this consumption level, this country's IVIG self-sufficieny level is only 6%. For Japan, the figures are 3.40 tons and 50% self-sufficieny level, and for China, 76.62 tons and 18%.

ALBUMIN

Table 4 (pg. 36) shows the consumption of albumin in 15 countries (column a), the volume of plasma for fractionation, both recovered and source (column b), the theoretical production of albumin based on the volume of plasma available, using a yield of 26 grams per liter (column c), and the self-sufficiency ratio in albumin production (column d) as percentage of the data in column (C) over those of column (a).

Illustrating *Table 4* (pg. 36) shows the self-sufficiency ratios in the fifteen countries under review. Similar observations and conclusions can be drawn from the albumin data as IVIG/SCIG. The average ratio of self-sufficiency of the fifteen countries is 171% but only 63% when excluding the five main countries supplying plasma for fractionation.



The data emphasize that self-sufficiency must be well defined and characterized in order to allow proper international comparisons.

Based on the current average consumptions of albumin, a similar model can be built with albumin as with IVIG, *Chart 2* (pg. 38) shows that the self-sufficiency level is a function of the average consumption per inhabitant. However, since there are alternative therapies and products possibly replacing albumin, and it is not the market driver, except in China, Japan and Asia in general, the self-sufficiency issue is more relevant in that part of the world than in the west.

Table 5 (pg. 37) assumes that all the countries under review would have the same average consumption level of 270 kilograms per million inhabitant. Under this scenario, the ranking of countries based on their self-sufficiency level with respect to albumin procurement only changes slightly in Europe but more significantly in Asia, where China's self-sufficiency drops from 48% to 27%, and India's from 24% to only 1%. The United States displaces the Czech Republic as the highest-ranking country with regard to self-sufficiency in albumin procurement, followed by Austria and Germany. This model pushes up the self-sufficiency level of those countries which have a comparatively high albumin consumption average, such as Italy (from 54% to 118%), while Japan's level does not change much (from 70% to 73%) because its consumption averages 280.6 kilograms per million inhabitants, which does not differ much from the level assumed in the model.

FACTOR VIII (PLASMA-DERIVED)

Table 6 (pg. 37) shows the consumption of plasma-derived factor VIII in 15 countries column (a), the volume of plasma for fractionation, both recovered and source column (b), the theoretical production of plasma-derived factor VIII based on the volume of plasma available, using a yield of 180 international units per liter column (c), and the self-sufficiency ratio in factor VIII production column (d) as percentage of the data in column (c) over those in column (a).

The case of plasma-derived factor VIII differs markedly from those of IVIG/SCIG and albumin because of the large and growing share of recombinant factor VIII, which has replaced plasma-derived products in many of the fifteen countries under review.

The concept of self-sufficiency in the procurement of plasma-derived factor VIII is obsolete in such countries as Canada, where the quantity of plasma-derived factor VIII used is negligible, and even the United States. Furthermore, the theoretical quantity of plasma-derived factor VIII does not represent the market reality because several countries do not produce factor VIII at all (Czech Republic, Mexico). The case of China is special because only a handful of fractionators produce plasma-derived factor VIII, and most of the source plasma collected in this country is not processed into factor VIII.

Table 6 (pg. 37) underlines the fact that several countries in which recombinant factor VIII dominates the market have large quantities of plasma-derived factor VIII available for other markets, mainly in countries where the healthcare funding agencies and/or patients or cannot afford the more expensive recombinant products.

CONCLUSION

Self-sufficiency in the procurement of IVIG/SCIG will increasingly be challenging in many countries as new patients are diagnosed and prescribed IVIG. The continued growth of IVIG consumption will put pressure on the plasma-collecting organizations, whether non-profit or commercial. The data emphasize that self-sufficiency must be well defined and characterized in order to allow proper international comparisons. Albumin consumption will be subjected to a similar trend, particularly in China and other Asia countries, whereas plasma-derived factor VIII will no longer be an important factor in the self-sufficiency debate, as it will increasingly be replaced by recombinant products. •

PATRICK ROBERT, *The Marketing Research Bureau, Inc.*

TABLE 1

Consumption and Potential Production of IVIG/SCIG in Selected Countries 2010–2013

Country	IVIG/SCIG Kilograms Consumed (a)	Plasma for Fractionation Liters (000) (b)	IVIG Production based on Plasma available 4 grams/Liter (c)	IVIG Self-Sufficiency Ratio in (%) (c)/(a)
Austria (2011)	770	470	1,880	244%
Brazil (2010)	1,785	150	600	34%
Canada (2012/13)	5,880	243	972	17%
China (2012)	15,000	3,800	15,200	101%
Czech Republic (2011)	295	350	1,400	475%
France (2011)	6,360	1,020	4,080	64%
Germany (2012)	5,640	2,940	11,760	209%
Greece (2011)	380	20	80	21%
India (2012)	1,390	160	640	46%
Italy (2011)	3,683	750	3,000	81%
Japan (2012)	4,230	960	3,840	91%
Mexico (2010)	950	20	80	8%
Russia (2011)	578	374	1,496	259%
Spain (2011)	2,950	340	1,360	46%
United States (2012)	52,930	23,730	94,920	179%
TOTAL	**102,821**	**35,327**	**141,308**	**137%**
Without the US	49,891	11,597	46,388	93%
Without US, A, D, CZ, China	28,186	4,037	16,148	57%

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TABLE 2

Average Consumption of IVIG/SCIG, Albumin and Factor VIII in Selected Countries

Country	Consumption of IVIG/ SCIG Per million Inhabitants (Kg./MM)	Consumption of Albumin Per million Inhabitants (Kg./MM)	Consumption of Recomb & pd Factor VIII Per Inhabitant (IUs/Capita)	Population (MM)
Austria (2011)	91.6	273.2	5.6	8.4
Brazil (2010)	10.0	75.6	2.4	179.2
Canada (2012/13)	168.0	283.3	5.7	34.9
China (2012)	10.9	148.6	0.1	1,377.1
Czech Republic (2011)	27.8	105.3	3.9	10.6
France (2011)	111.0	278.9	6.3	63.5
Germany (2012)	68.0	180.0	7.9	81.7
Greece (2011)	38.0	611.5	3.3	10.8
India (2012)	1.3	14.1	0.0	1,237.0
Italy (2011)	59.8	623.3	7.3	61.0
Japan (2012)	33.2	280.6	4.0	127.3
Mexico (2010)	8.4	73.1	0.6	113.4
Russia (2011)	4.1	52.0	5.3	142.5
Spain (2011)	62.9	299.6	4.5	46.8
United States (2012)	169.1	461.7	7.6	313.2
TOTAL/AVERAGE				**3,807.2**

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TABLE 3

Self Sufficiency Levels in IVIG Procurement in Fifteen Countries Based on Current Demand and Theoretical 60 Kg/M Inhabitant Demand Level

Country	Population (MM)	Theoretical IVIG/SCIG Kg. Consumed 60 Kg.MM Pop (a)	Reported IVIG/SCIG Kilograms Consumed (b)	Difference (b)-(a) Surplus or Deficit (ii)	IVIG Production based on Plasma available 4 grams/Liter (c)	Currently reported IVIG Self-Sufficiency Ratio in Percent (c)/(b)	Theoretical IVIG Self-Suff. Ratio (%) 60 Kg.MM Pop (c)/(a)
Austria (2011)	8.4	505	770	265	1,880	244%	372%
Brazil (2010)	179.2	10,751	1,785	(8,966)	600	34%	6%
Canada (2012/13)	34.9	2,094	5,880	3,786	972	17%	46%
China (2012)	1,377.1	82,624	15,000	(67,624)	15,200	101%	18%
Czech Republic (2011)	10.6	634	295	(339)	1,400	475%	221%
France (2011)	63.5	3,807	6,360	2,553	4,080	64%	107%
Germany (2012)	81.7	4,904	5,640	736	11,760	209%	240%
Greece (2011)	10.8	646	380	(266)	80	21%	12%
India (2012)	1,237.0	74,220	1,390	(72,830)	640	46%	1%
Italy (2011)	61.0	3,658	3,683	25	3,000	81%	82%
Japan (2012)	127.3	7,635	4,230	(3,405)	3,840	91%	50%
Mexico (2010)	113.4	6,805	950	(5,855)	80	8%	1%
Russia (2011)	142.5	8,552	578	(7,974)	1,496	259%	17%
Spain (2011)	46.8	2,806	2,950	144	1,360	46%	48%
United States (2012)	313.2	18,792	52,930	34,138	94,920	179%	505%
TOTAL/AVERAGE	**3,807.2**	**228,433**	**102,821**	**(125,612)**	**141,308**	**137%**	**62%**

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TABLE 4

Consumption and Potential Production of Albumin in Selected Countries

Country	Albumin Kilograms Consumed (a)	Plasma for Fractionation Liters (000) (b)	Albumin Production based on Plasma available 26 grams/Liter (c)	Albumin Self-Sufficiency Ratio in (%) (c)/(a)
Austria (2011)	2,300	470	12,220	531%
Brazil (2010)	13,550	150	3,900	29%
Canada (2012/13)	9,890	243	6,318	64%
China (2012)	205,600	3,800	98,800	48%
Czech Republic (2011)	1,113	350	9,100	818%
France (2011)	17,700	1,020	26,520	150%
Germany (2012)	16,070	2,940	76,440	476%
Greece (2011)	6,580	20	520	8%
India (2012)	17,400	160	4,160	24%
Italy (2011)	36,442	750	19,500	54%
Japan (2012)	35,700	960	24,960	70%
Mexico (2010)	8,110	20	520	6%
Russia (2011)	7,411	374	9,724	131%
Spain (2011)	14,013	340	8,840	63%
United States (2012)	144,500	23,730	616,980	427%
AVERAGE	**536,379**	**35,327**	**918,502**	**171%**
Without the US	391,879	11,597	301,522	77%
Without US, A, D, CZ, China	166,796	4,037	104,962	63%

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TABLE 5

Self Sufficiency Levels in Albumin Procurement in Fifteen Countries Based on Current Demand and Theoretical 270 Kg/M Inhabitant Demand Level

Country	Population (MM)	Theoretical Albumin Kg. Consumed 270 Kg.MM Pop (a)	Reported Albumin Kilograms Consumed (b)	Difference (b)-(a) Surplus or Deficit (ii)	Albumin Production based on Plasma available 26 grams/Liter	Currently reported IVIG Self-Sufficiency Ratio in Percent (c)/(b)	Theoretical Albumin Self-Suff. Ratio (%) 270 Kg.MM Pop (c)/(a)
Austria (2011)	8.4	2,273	2300	27	12,220	531%	538%
Brazil (2010)	179.2	48,381	13,550	(34,831)	3,900	29%	8%
Canada (2012/13)	34.9	9,423	9,890	467	6,318	64%	67%
China (2012)	1,377.1	371,808	205,600	(166,208)	98,800	48%	27%
Czech Republic (2011)	10.6	2,853	1,113	(1,740)	9,100	818%	319%
France (2011)	63.5	17,134	17,700	566	26,520	150%	155%
Germany (2012)	81.7	22,067	16,070	(5,997)	76,440	476%	346%
Greece (2011)	10.8	2,905	6,580	3,675	520	8%	18%
India (2012)	1,237.0	333,990	17,400	(316,590)	4,160	24%	1%
Italy (2011)	61.0	16,460	36,442	19,982	19,500	54%	118%
Japan (2012)	127.3	34,358	35,700	1,343	24,960	70%	73%
Mexico (2010)	113.4	30,624	8,110	(22,514)	520	6%	2%
Russia (2011)	142.5	38,482	7,411	(31,071)	9,724	131%	25%
Spain (2011)	46.8	12,628	14,013	1,385	8,840	63%	70%
United States (2012)	313.2	84,564	144,500	59,936	616,980	427%	730%
TOTAL/AVERAGE	**3,807.2**	**1,027,949.9**	**536,379**	**(491,571)**	**918,502**	**171%**	**89%**

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TABLE 6

Consumption and Potential Production of Plasma-derived Within Selected Countries

Country	Plasma-derived Factor VIII IUs (MM) Consumed (a)	Plasma for Fractionation Liters (000) (b)	FVIII Production based on Plasma available 180 IUs/ Liter (c)	Factor VIII Self-Sufficiency Ratio in (%) (c)/(a)
Austria (2011)	15.0	470	84.6	564%
Brazil (2010)	425.0	150	27.0	6%
Canada (2012/13)	0.3	243	43.7	14110%
China (2012)	5.9	3,800	684.0	NA
Czech Republic	36.0	350	63.0	175%
France (2011)	63.0	1,020	183.6	291%
Germany (2012)	281.0	2,940	529.2	188%
Greece (2011)	2.5	20	3.6	144%
India (2012)	38.2	160	28.8	75%
Italy (2011)	91.9	750	135.0	147%
Japan (2012)	84.2	960	172.8	205%
Mexico (2010)	65.5	20	3.6	5%
Russia (2011)	675.0	374	67.3	10%
Spain (2011)	70.0	340	61.2	87%
United States (2012)	360.0	23,730	4,271.4	1187%
AVERAGE	**2,213.5**	**35,327**	**6,358.9**	**287%**
Without the US	1,853	11,597	2,087	113%
Without US, A, D, CZ, China	1,516	4,037	727	48%

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CHART 1

Average IVIG/SCIG Consumption by Country (Kilograms per Million People)

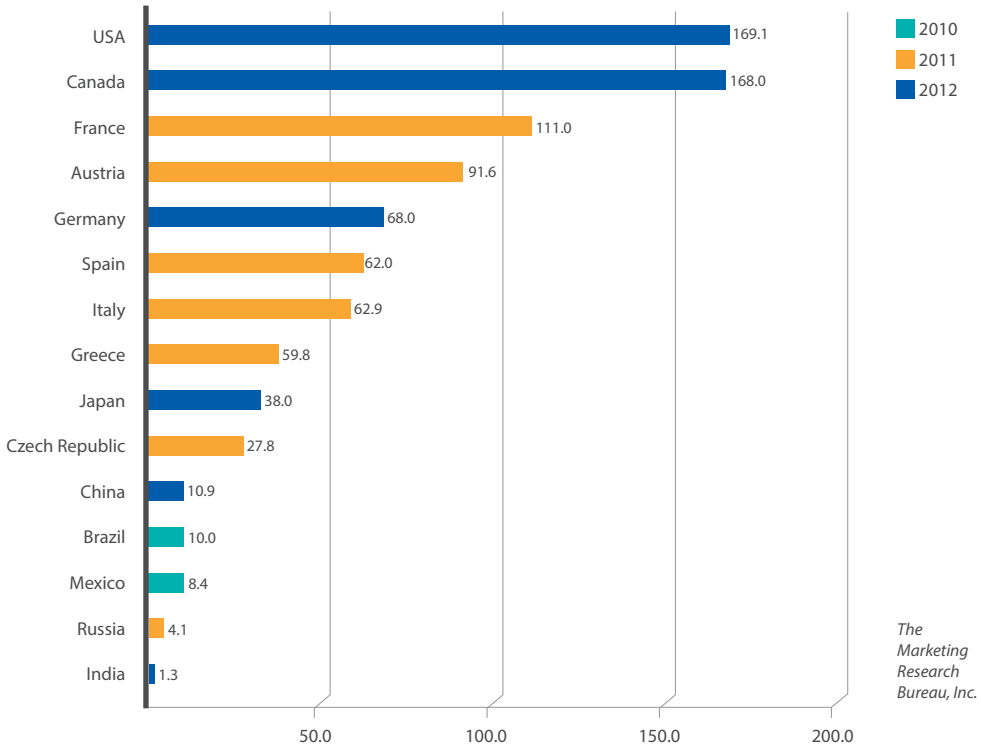

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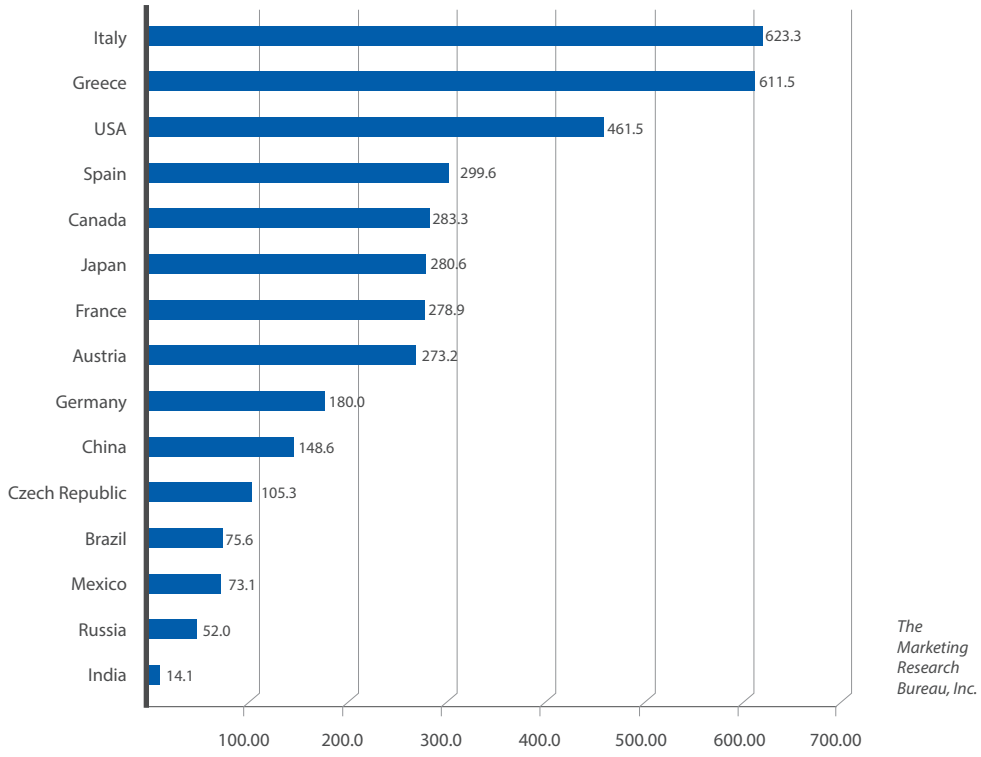
CHART 2

Average Albumin Consumption by Country 2010/2012 (Kilograms per Million People)



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GLOSSARY OF TERMS

AFRO	WHO REGIONAL OFFICE FOR AFRICA
AMRO	WHO REGIONAL OFFICE FOR THE AMERICAS
APLUS	AMERICAN PLASMA USERS COALITION
CBS	CANADIAN BLOOD SERVICES
CGMP	CURRENT GOOD MANUFACTURING PROCEDURES
CPR	CANADIAN PLASMA RESOURCES
DG	DIRECTOR GENERAL
EB	EXECUTIVE BOARD
EBA	EUROPEAN BLOOD ALLIANCE
ECBS	EXPERT COMMITTEE ON BIOLOGICAL STABILIZATION
EMA	EUROPEAN MEDICINES AGENCY
EMRO	WHO REGIONAL OFFICE FOR THE EASTERN MEDITERRANEAN
EQAS	EXTERNAL QUALITY ASSESSMENT SCHEMES
EURO	WHO REGIONAL OFFICE FOR EUROPE
FDA	U.S. FOOD AND DRUG ADMINISTRATION
FIODS	FÉDÉRATION INTERNATIONALE DES ORGANISATIONS DE DONNEURS DE SANG
IG	IMMUNOGLOBULIN
IPFA	INTERNATIONAL PLASMA FRACTIONATION ASSOCIATION
IQPP	INTERNATIONAL QUALITY OF PLASMA PROGRAM
ISBT	INTERNATIONAL SOCIETY BLOOD TRANFUSION
ITP	IDIOPATHIC THROMBOCYTOPENIC PURPURA
IU	INTERNATIONAL UNIT
IVIG	INTRAVENOUS IMMUNOGLOBULIN
IVIG/SCIG	INTRAVENOUS AND SUBCUTANEOUS IMMUNE GLOBULIN
MRB	MARKETING RESEARCH BUREAU
NDDR	NATIONAL DONOR DEFERRAL REGISTRY
NDP	NEW DEMOCRATIC PARTY
NGO	NON-GOVERNMENTAL ORGANIZATION
NRBDO	NETWORK OF RARE BLOOD DISORDER ORGANIZATIONS
PAHO	PAN AMERICAN SANITARY BUREAU
PDMP	PLASMA DERIVED MEDICINAL PRODUCTS
PID	PRIMARY IMMUNODEFICIENCIES
PLUS	PLATFORM OF PLASMA PROTEIN USERS
PPTA	PLASMA PROTEIN THERAPEUTICS ASSOCIATION
PPTs	PLASMA PROTEIN THERAPIES
PSC	PROGRAMME SUPPORT COST
QSEAL	QUALITY STANDARDS OF EXCELLENCE, ASSURANCE AND LEADERSHIP
SEARO	WHO REGIONAL OFFICE FOR SOUTH-EAST ASIA
TRS	TECHNICAL REPORT SERIES
VCJD	VARIANT CREUTZFELDT-JAKOB DISEASE
VNRBD	VOLUNTARY, NON-REMUNERATED BLOOD DONATION
VNRD	VOLUNTARY, NON-REMUNERATED DONATION
WHA	WORLD HEALTH ASSEMBLY
WHO	WORLD HEALTH ORGANIZATION
WIP	WORK-IN-PROGRESS
WPRO	WHO REGIONAL OFFICE FOR THE WESTERN PACIFIC
WR	WHO REPRESENTATIVE


Edinburgh, Scotland

Upcoming Events

CONFERENCES & SYMPOSIUMS

October

26 PPTA Business Forum (Invitation Only)
Philadelphia, Pennsylvania

27–31 Haemophilia Academy 2014
Edinburgh, Scotland, United Kingdom

28–Nov 1 IPOPI/INGID/ESID Biennial Meeting 2014
Prague, Czech Republic

30–Nov 2 Congress on Controversies in Thrombosis & Hemostasis (CiTH)
Berlin, Germany

31–Nov 2 76th Annual Meeting of Japanese Society of Hematology
Osaka, Japan

November

6–7 American Thrombosis and Hemostasis Network Data Summit
Chicago, Illinois

6–8 5th Transfusion Medicine Congress in Belgrade
Belgrade, Serbia

12–14 5th Annual World Orphan Drug Congress Europe 2014
Brussels, Belgium

20–22 Portugese Society of Hematology Annual Meeting 2014
Évora, Portugal

26–28 Australian Vascular Biology Society 2014 Scientific Meeting
Adelaide, Australia

27–28 Belgian Society of Thrombosis and Haemostasis 22nd Annual Meeting
Mechelen, Belgium

December

6–9 56th Annual Meeting and Exposition of the American Society of Hematology
San Francisco, California

March 2015

10–11 International Plasma Protein Congress (IPPC)
Rome, Italy

June 2015

16–17 Plasma Protein Forum
Washington, DC

Sept 2015

1–3 Bioplasma World Asia Conference
Shanghai, China

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