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1425 Rene Levesque W. Suite 1010
Montreal, Quebec, H3G 1T7 Canada

Tel: 1(514) 875-7944
Fax: 1(514) 875-8916
Email: wfh@wfh.org
Internet: www.wfh.org

World Federation of Hemophilia 3rd Global Forum on the Safety and Supply of Hemophilia Treatment Products



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Table of Contents

Executive Summary	1
Defining the Debate: Access, Donor Remuneration, and Self-Sufficiency	1
Emerging Safety and Supply Issues	2
Safety and Supply Issues: Paid/Unpaid Donors	3
Self-Sufficiency in Emerging Markets	4
Self-Sufficiency in Established Markets	4
Closing Discussion	5
 Welcome and Introductions	 7
 Defining the Debate: Access, Donor Remuneration, and Self-Sufficiency	 8
Self-Sufficiency—Historical Perspective and Perceptions	8
What is Self-Sufficiency for Hemophilia?	9
Self-Sufficiency: Evolution of an International Concept	10
Blood Safety and Sufficiency—The Efforts of the Global Collaboration for Blood Safety	11
Plenary Discussion	13
 The Economics of Self-Sufficiency	 14
Trends in the Global Blood Products Market: WTO, EU Rules, and the Effect of Recombinant	
Products on World Supply	14
Domestic and Contract Plasma Fractionation Programs: Economic Aspects and Impacts	
on Local Hemophilia Care	16
Plenary Discussion	17
 Self-Sufficiency and Fractionation in Emerging Markets	 18
How Are the Issues Defined?	18
Choosing Between the Options: Brazil	19
Choosing Between the Options: South Africa	20
Choosing Between the Options: India	21
Choosing Between The Options: China	22
Plenary Discussion	23

(continued next page)

Table of Contents *(continued)*

Emerging Safety and Supply Issues	25
Challenges to the Bleeding Disorders Community	25
Update on vCJD	26
Safety Aspects of Locally Made Small Pool Hemophilia Treatment Products (Cryoprecipitate)	27
Plenary Discussion	28
 Open Forum Discussion	 29
 Paid/Unpaid Donors: Safety and Supply Issues	 33
Paid/Unpaid Donors and Safety	33
Paid/Unpaid Donors and Supply	34
Paid/Unpaid Donors and Supply	35
Plenary Discussion	36
 Self-Sufficiency in Plasma and Fractionation in Established Markets	 37
Self-Sufficiency in Established Markets	37
Our Common Goal: Access to Safe and Reliable Product Supply	38
Self-Sufficiency in Japan	40
The Australian Approach to Self-Sufficiency	41
Plenary Discussion	42
 Closing Plenary Discussion	 44



Executive Summary

The World Federation of Hemophilia's third global forum focused on plasma-derived factor concentrates, including product safety and supply, access, self-sufficiency, and donor remuneration. Forum chair David Page, WFH Vice-President for National Member Organizations (NMOs), and chair of the WFH blood safety, supply, and availability committee, opened the forum with the following questions:

Is having enough plasma for national needs a desirable goal?

Yes: 76%
No opinion: 4%
No: 20%

Is having enough fractionation capacity for national needs a desirable goal?

Yes: 47%
No opinion: 6%
No: 47%

Is having both enough plasma and enough fractionation capacity for national needs a desirable goal?

Yes: 58%
No opinion: 0%
No: 42

Which is safer?

Paid plasma: 11%
Unpaid plasma: 45%
No difference: 45%

Defining the Debate: Access, Donor Remuneration, and Self-Sufficiency

Brian O'Mahony, President of the WFH, presented a personal perspective on the emergence of self-sufficiency, access to therapy, and donor remuneration as critical issues around the world. Mr. O'Mahony said that, given the reality that there are 300,000 people in the world who have hemophilia and who do not have access to any treatment, let alone plasma or recombinant

products, solutions cannot be unequivocal. "There is very little point in having a very safe, efficacious product if it is not available or if a country can't afford it. Safety, supply, and affordability need to be seen as part of the same equation," Mr. O'Mahony stated. "We must decide not to make our decisions based on political considerations, national situations and unrealistic aspirations and timelines—these decisions should be based on data and reality, not sentiment."

Dr. Bruce Evatt of the Hereditary Blood Disorders Division, Centers for Disease Control (CDC), U.S.A. said that, while blood safety is of primary importance in the developed world, it also has consequences in the developing world, where availability of supply remains the paramount issue. Developing countries face significant barriers tied to availability, costs, regulations, and basic manufacturing resources. "Supply remains the basic deficiency for most hemophilia patients in the developing parts of the world, where the shortage of clotting factors remains the primary risk," he said.

Dr. Albert Farrugia, head of Blood and Tissue Services, Australian Commonwealth Therapeutic Goods Administration, said the underlying concepts of self-sufficiency are to prevent the exploitation of third-world donors by commercial blood collection agencies, encourage development of blood services in developing countries, and address the high risk of transfusion transmissible markers in paid donor populations. "I believe that safety is not a function of whether you are self-sufficient or not, nor is it a function of whether donors are remunerated or not—it's a function of the whole system of blood collection, testing, manufacturing, and regulation." Most of the world doesn't have enough blood, and economic and political arguments should not be used to cloud the real issue at hand, getting blood products to the people who need them.

Dr. Jay Epstein of the Office of Blood Research and Review, U.S. Food and Drug Administration (FDA), explained the rationale behind the Global Collaboration for Blood Safety (GCBS). The GCBS working group on policy process is working on developing a model for decision-making for blood. Another working group is focussing on the plasma issues in blood safety, providing guidance on national decision-making and promoting the transfer of technology. A third working group is focussing on quality assessment and assistance for development. It is working to develop generic global minimum requirements for blood transfusion



services for consideration by the World Health Organization (WHO).

The Economics of Self-Sufficiency

Jan Bult, President, Plasma Proteins Therapeutic Association (PPTA), said that, in North America, 70% of the product used is recombinant. In the European Union, nearly 60% is recombinant, while Japan uses over 50% recombinant. It is critical to understand that both plasma-derived and recombinant products are safe. He stressed that product availability and accessibility is also a safety issue and predicted there would be the need for both therapies for the next several decades. Mr Bult also discussed some artificial barriers to market access, including those in Belgium, Denmark, France, Taiwan, and Japan.

Dr. Thierry Burnouf, Director, Human Plasma Product Services, examined whether or not domestic or contract fractionation are safe, viable, efficient ways to provide good products and improve the access to high quality care for hemophilia populations, particularly in the developing world. The crucial element in choosing between contract and domestic fractionation, he concluded, is the plasma price and the current availability of source material. Product portfolio is also important, since the cost of factor VIII is linked to the demand for other products. Yield and batch size are also important, as are construction and local regulatory costs. He reminded participants that there continues to be a significant difference between the technology necessary for the production of standard drugs and biopharmaceuticals.

Emerging Safety and Supply Issues

Mark W. Skinner, of the National Hemophilia Foundation, U.S.A., said the complexities of the supply issue are becoming better understood. In the developed world, a major shortage of recombinant products, which are viewed as luxuries in most parts of the world, has already been experienced. That, in turn, prompted a worldwide shortage of plasma products as they were diverted back to developed countries. Even recent events, like the seroconversion of a plasma donor in New Zealand, can cause local shortages. "In our zeal for advanced safety, if we don't make some compromises, we're all in jeopardy of having no product to treat with,"

he said. The concern about adequate affordable supply is shared between the developed and developing worlds.

Dr. Evatt said that Creutzfeldt-Jakob Disease (CJD) and variant Creutzfeldt-Jakob Disease (vCJD) have both created major disruptions in the plasma derivatives markets and in the availability of supply. Investigators have come to the conclusion that classic CJD presents little or no risk of being transmitted through plasma or plasma products. In addition, a number of studies have determined that current methods for FVIII preparation remove 3 to 6 logs of vCJD, while FIX preparation methods clear 7 logs. While it is still widely accepted that it's possible to transmit vCJD through blood transfusions, the probability of transmission is extremely small with plasma derivatives. Continued vigilance and active surveillance are necessary, he concluded, but the lack of transmission evidence to date suggests that vCJD is of less concern than some of the new emerging agents.

Dr. Farrugia noted that cryoprecipitate continues to be a significant product, particularly in the developing world. There are several features affecting the quality of cryoprecipitate, including the need to optimize FVIII yield, minimize the fibrinogen and general protein content, and create products that are presented in the most convenient way possible. Cryoprecipitate's resistance to viral inactivation techniques poses a more difficult problem, he said. In order to address these concerns, the WFH has established a Safe Cryo Project, which will review cryo use and production from the perspective of quality and safety. Dr. Farrugia concluded that small pool freeze-dried cryoprecipitate is a viable option for treatment in countries that lack the access to, or financial means for, fractionation. Since product safety can't be ensured through viral inactivation, he reiterated the importance of donor selection and screening measures.

Are you less concerned about transmissibility of vCJD than you were two years ago?

Yes: 81%
No Opinion: 2%
No: 17%

Is it worthwhile to pursue safer cryoprecipitate?

Yes: 72%
No opinion: 2%
No: 26%



If safe cryoprecipitate could be developed, would it be more affordable than current factor concentrates?

Yes: 48%

No opinion: 19%

No: 33%

Safety and Supply Issues: Paid/Unpaid Donors

Dr. Theo Buunen, President of the European Plasma Fractionation Association (EPFA), discussed studies on the safety of paid versus unpaid donations. The introduction of initiatives such as qualified donors and inventory holds, will reduce the risk of an infectious unit being included in a plasma pool, but even so, a higher risk in paid donors remains, Dr. Buunen said. "The ultimate safety level for finished plasma products is still a matter of debate and needs further analysis, principally because inactivation data are very different for different virus types and production procedures vary."

Dr. George Schreiber of Westat said that, rather than donor remuneration, the real issues in the treatment of hemophilia involve whether the plasma pool is equal to whole blood, and source plasma to recovered plasma. While testing helps shrink risk, viral inactivation is key to safer products. Noting that source plasma donors give about 17 times a year, Dr. Schreiber suggested that removing remuneration would result in product shortages that could not be made up for through unpaid donors, particularly given the spot shortages in fresh components that the U.S. already experiences occasionally. For HIV, HCV, and HBV, the risk of having a potentially contaminated manufacturing pool is of the same order of magnitude for source and recovered plasma, and for remunerated and non-remunerated donations. When subject to proper screening, there is no evidence of any difference in safety between remunerated and non-remunerated products, he concluded.

Charles Waller, of the PPTA, said that, without compensating donors, not enough plasma will be collected. About 23 million litres of plasma are collected for fractionation yearly. About 14 million litres of the plasma collected for fractionation comes from donors who receive some form of compensation for their time. To meet demand, many new donors will be needed in order to double the current quantity of plasma for fractionation. This

will translate into one million new plasma donors and more than 37 million new blood donors, Mr. Waller said. Given the conclusions regarding the safety of compensated plasma donors and the importance of viral inactivation and regulation, the hemophilia community needs to focus on the pressing issue of supply, rather than remuneration, he concluded.

Dr. Jukka Rautonen, of Red Cross Finland, said the safety of blood derivative products depends on a chain of activities that includes donor selection, aseptic collection, screening tests, the production process, adequate storage, and usage patterns. The question of remuneration is only one part of the donor selection process, Dr. Rautonen suggested. Even if the idea that using unpaid donors would be beneficial is accepted, there is a need to determine whether this is possible. He noted that the frequency of blood donations per capita is consistently higher in developed countries with non-remunerated donations. Rather than debate remuneration, hemophilia stakeholders should work together to decide where the limited resources are needed, he concluded.

Self-Sufficiency in Emerging Markets

Citing a 2001 WFH survey, Dr. Alok Srivastava, Christian Medical College, India, stated that, regardless of economic status, there is a direct correlation in the life expectancy of people with hemophilia and the number of hemophilia treatment centres in their country. There is also a strong correlation between musculo-skeletal function and the use of factor concentrates. Dr. Srivastava asked if those industries looking at the global market can provide factor concentrates to meet these needs at costs affordable to developing countries, and yet still be attractive and viable enough for the manufacturer. Dr. Srivastava also asked if there is a lack of resources in developing countries, or if there is a skewed distribution of what's available.

Dr. Luiz Amorim, of HEMORIO, said that, in Brazil, it is forbidden to sell blood, blood components, and blood derivatives. Dr. Amorim explained that Hemophilia A is treated with cryoprecipitate, with close to 15% treated with locally produced low purity FVIII. Hemophilia B is treated with fresh frozen plasma or prothrombin complex, and von Willebrand disease is treated with cryoprecipitate.



Brazil's effort towards self-sufficiency in plasma derivatives began with contract fractionation and involves the construction of a plasma fractionation centre with a capacity of 500,000 litres annually. However, self-sufficiency should not be seen as a barrier for importing blood products and, he added, Brazil intends to have local production and self-sufficiency in 10 to 20 years and will stop importation only if needed.

Dr. Duncan Armstrong of Natal BioProducts Institute discussed the South African experience. Production of plasma products is based on voluntary donors for whole blood and plasmapheresis. All donations are viral-marker screened and component preparation is made from more than 95% of the donations collected. Plasma safety is dependent on the source of the blood and processes such as donor selection, testing, cGMP and compliance with regulations. The financial impact of alternative products is quite complex because of the close interaction between transfusion and fractionation, Dr. Armstrong noted. Any loss in terms of revenue from plasma to fractionation will lead to an increase in red cell/platelet prices. Imported products would reduce the cost effectiveness of fractionation.

Dr. Urmish Chudgar of the Advanced Transfusion Medicine and Research Foundation, India, said a large number of patients depend on cryoprecipitate, fresh plasma, and even fresh whole blood. Most of the blood banks depend on "replacement" donors who must be recruited by the patient who uses the blood products. Although the donors are very high-risk, a study showed that 87% of blood banks depend on replacement donors. Only 47% had componentization facilities and, while all blood banks had testing in place for HIV, HbsAg, and HCV, none had proper quality control and assessment systems. Until India has FVIII or FIX or fractionation capacity, its options are to import plasma products (a current practice at cost of \$52 million); to develop products at blood banks; contract fractionation; or set up plasma fractionation facilities.

In discussion, Mr. O'Mahony said adequate care is impossible to define. "But if you go from 0.5 to 1, and then 1 to 2 units per capita, you get a fivefold increase in survival. As you go beyond 2, you get more functional independence, and at 4, 5, or 6 units per capita, you start getting joint integrity. In every country that the WFH goes into, we try to look where they are and take the next step. You

can't go from 0 to 6, but you can go from 0.5 to 1, and take things in sequence."

Self-Sufficiency in Established Markets

Dr. Buunen said that in developed countries the limitations of supply are often due to limited national or personal healthcare budgets, just as they are in developing nations. He said most nations base their self-sufficiency policies on several key elements. Source material is usually collected by a single organization under government regulation or supervision and there tends to be a single manufacturer. Import restrictions are put in place for safety reasons, to safeguard supply or to protect the role of the sole manufacturer. Dr. Buunen conceded there are several serious disadvantages to this approach. A single source supplier limits the choice of products and the supply is vulnerable in the event of safety incidents or production problems. The lack of competition inhibits innovation. There is a role for "sufficiency" policies, but not for "self-sufficiency" in the single-source classic sense, he concluded.

Dr. Ruedi Wäger, CEO and President, Aventis Behring, said that very slow-moving scientific investigation, lagging medical judgment, and a lack of proactive response on the part of the industry led to a disaster in the 1980s. Since that time, the most innovative technologies, such as heat treatment, PCR testing, and novel products, have come from large commercial companies. Dr. Wäger stressed the importance of open dialogue between all stakeholders, including patients, manufacturers, scientists, and legislators. Compensation is one way of encouraging healthy donors to make repeat donations. Repeat donors are an integral part of the quality and safety process, without which product supply would be severely restricted.

Jugo Hanai, Director, Medical Care and Human Rights Network, Japan, said historic events led to the most recent changes in the Japanese blood laws. Mr. Hanai explained that the Act for Securing the Stable and Safe Supply of Blood defines self-sufficiency as meaning that, "blood products for domestic consumption are manufactured using source material that is voluntary, non-remunerated, and from within the country." An important breakthrough, he said, is that the committee which oversees much of the regulatory regime has two hemophilia patients on it.



Dr. Farrugia said the concept of Australian self-sufficiency originated in the World Health Assembly resolution, but the real issue is the fear of overseas pathogens. Australia also protected its biotechnology sector, but he stressed that this was never at the expense of patient care. In 2003, a government working party on rFVIII and rFIX, recommended that the national supply target 3.31 IU per capita for FVIII; that current restrictions on access to rFVIII and rFIX be removed as rapidly as possible; and that a target of 85% recombinant use be reached as soon as possible. Self-sufficiency is understandable and enshrined within the Australian system, Dr. Farrugia said. In recent years, however, the approach has become more flexible, and rather than restricting the regulator's powers, the commitment to self-sufficiency has enhanced them.

During open discussion, a participant noted Dr. Wäger's statement that global regulatory harmonization could result in 15% to 20% cost reductions. He asked if this would translate to a corresponding reduction in product prices. Dr. Wäger said that plasma fractionation is an extremely complicated process. Cutting out regulatory complexities would certainly benefit the whole industry, he said, but price depends on individual companies and what the situation is at any given time.

Forum participants discussed the issue of the number of plasma fractionators decreasing while the companies still involved get larger and larger. Mr. Waller said that companies tend to consolidate when they can make more profit together than they can individually. The low profitability in the industry means more consolidation, which results in fewer product choices for patients. More providers mean a more vibrant industry that can commit resources to meet new challenges like WNV. Dr. Epstein said that it is more difficult to regulate sole-source manufacturers. The ultimate impact on the consumer is adverse because the industry is less robust and because there will tend to be less innovation and, therefore, less product choice.

Closing Discussion

Mr. O'Mahony polled the audience on a number of questions aimed at gauging changes of perception or opinion since the start of the forum, and perspectives on future issues.

Is having enough fractionation capacity for national needs a desirable goal?

Yes: 51%
No Opinion: 4%
No: 45%

Is having both plasma and enough fractionation capacity for national needs a desirable goal?

Yes: 58%
No Opinion: 1%
No: 40%

Which is safer?

Paid: 10%
Unpaid: 31%
No Difference: 60%

What is the most critical issue facing the hemophilia community?

Safety: 26%
Supply: 26%
Affordability: 48%

Mr. O'Mahony noted that a slight increase of participants now saw fractionation capacity to meet national needs as a desirable goal. However, there was no proportional change in viewpoint on having both plasma and enough fractionation capacity for national needs as a desirable goal. He noted a significant increase in the proportion of participants who felt there was no difference between the safety of paid and unpaid donations. Most interestingly, he said, the position among participants had shifted over the course of the forum, and it was now felt that safety and supply were of equal importance and that affordability is becoming the biggest issue.

Dr. Evatt noted that the principles of self-sufficiency and voluntary donors were established in a different time. Since then, the dramatic expansion of technologies has changed the reality of the issue. He added that no evidence has been presented showing that principles of self-sufficiency and voluntary donations have actually increased blood collection



and capacity. In fact, he said, it is clear that in many places these principles have been barriers.

Dr. Epstein said the translation of self-sufficiency principles into practice is really dependent on local conditions. Noting the intersection between the efforts to make whole blood components safe and efforts to obtain safe plasma, he said, "There are settings where these are very tightly linked and if plasma collection becomes the driver, then the blood components become less safe. That interplay needs to be more carefully examined."

Dr. Srivastava said the issue of supply is inter-related with what is considered adequate treatment, since these standards determine the supply required. In 1996, for instance, 1 to 2 IU of factor per capita was considered a good volume, but in recent years this has risen to 2 to 5 IU per capita. This does not necessarily translate to better long-term outcomes, he noted. It is important to recognize that the current definition of what is optimal treatment will predict supply requirements.



Welcome and Introductions

David Page, Canadian Hemophilia Society

The aim of the World Federation of Hemophilia's third global forum was to encourage a genuine and open discussion on key issues including product safety and supply, access, self-sufficiency, and donor remuneration, said David Page, Vice-President of WFH NMOs, chair of the WFH blood safety and supply committee, and forum chairman. While previous fora had welcomed participants to Montreal, the third forum was being held in Budapest following a weekend workshop with regulators from central and eastern Europe during which participants examined the evaluation of clotting factor concentrates.

As at the 1999 and 2001 fora, participants represented a range of perspectives, including people with hemophilia, physicians, hemophilia societies, regulators, and industry. Organizers felt that the traditional voting procedure would capture audience opinion, as well as shifts in opinion over the course of the sessions and forum. Mr. Page launched the forum with the following questions:

What is national self-sufficiency? Participants voted:

Enough plasma for national needs: 47%
The fractionation capacity for national needs: 1%
Both enough plasma and enough fractionation capacity for national needs: 52%

Is having enough plasma for national needs a desirable goal?

Yes: 76%
No opinion: 4%
No: 20%

Is having enough fractionation capacity for national needs a desirable goal?

Yes: 47%
No opinion: 6%
No: 47%

Is having both enough plasma and enough fractionation capacity for national needs a desirable goal?

Yes: 58%
No opinion: 0%
No: 42%

Which is safer?

Paid plasma: 11%
Unpaid plasma: 45%
No difference: 45%



Defining the Debate: Access, Donor Remuneration, and Self-Sufficiency

Chair: David Page, Canadian Hemophilia Society

Self-Sufficiency—Historical Perspective and Perceptions

Brian O'Mahony, President of the World Federation of Hemophilia (WFH)

Mr. O'Mahony presented a personal perspective focusing on three significant points in time, around 1983, 1993, and 2003, when self-sufficiency, access to therapy, and donor remuneration emerged as critical—and controversial—issues around the world. The backdrop throughout this contentious debate has been the devastation of the hemophilia community globally due to infection with HIV and HCV.

In 1983, with the impact of HIV increasing and rising concerns about HIV infection through blood products, countries including France and Switzerland banned products manufactured from plasma collected from paid donors in the U.S., and debate on self-sufficiency and donor remuneration intensified. Yet, while the Council of Europe recommended the avoidance of the use of coagulation factor products prepared from large plasma pools, especially in countries where self-sufficiency had not yet been achieved, and that patients with hemophilia be informed of the potential health hazards, recommendations failed to be passed on in any concerted way. The failure to take concerted action increased the amount of fear and mistrust that developed, and has affected the debate over the past 20 years.

The debate also focused on the restriction of imports. In 1990, the Council of Europe promoted self-sufficiency on the basis of voluntary donors and guidelines for the “rational use of products.” This

caused enormous debate and concern that “rational use” actually referred to rationing. Mr. O'Mahony noted that usage in Europe ranged from 0.4 to 5.6 IU per capita, with average per capita use of 1.9 IU. The idea that “rational use” and self-sufficiency would mean the use of the average level of 1.9 IU per head raised alarm that future treatment of hemophilia would be dictated by the amount of plasma available for fractionation within a specific country or region, rather than by clinical needs, he explained. Mr. O'Mahony called the concept of average per capita use inconsequential since it ignores the enormous variations in unit usage per capita and different treatment protocols and regimes in different countries.

By 1993, the full devastation within the community due to HIV had become apparent, and HCV was becoming an increasing concern. Despite a European Union (EU) directive (89-381-ECC), increased self-sufficiency had not arisen and there was continued reliance on the importation of concentrates from plasma abroad, along with the realization that this would have immense impact on supply in Europe. A new EU directive (2002-98-EC) again promotes voluntary donations and self-sufficiency and includes measures to restrict the import of factor concentrates that are not manufactured from unpaid donors, Mr. O'Mahony said. Over the past 10 years, hemophilia organizations have become much more knowledgeable and focused on the issues. The community has experienced a number of severe shortages of plasma-derived and recombinant factor concentrates that have led to a greater realization of the link between safety and supply. Consequently, concerns have been expressed about 2002-98-EC over potential restriction of supply and choice.

Following consultations, the WFH, the European Hemophilia Consortium (EHC), and representatives from industry and the not-for-profit sectors have come to a common position, Mr. O'Mahony said. “While voluntary unpaid donors should be encouraged, it would be foolish and counter-productive to try to ban imports or inhibit supply in the absence of clear and real scientific data on safety.” The ban would be irrational in the U.K., for instance, which has had to import plasma from paid donors in the U.S. due to a theoretical risk of variant CJD from its own donor pool. Clear consultation mechanisms need to be in place, he added.

In the year 2003, the self-sufficiency debate continues in countries as diverse as Japan, Australia, Brazil, and China. Mr. O'Mahony stressed that the



debate must take place in a rational manner, looking at the clinical requirements for treatment, rather than simply the amount of plasma being collected. There is now knowledge of the risk of cryoprecipitate, particularly in countries where there is high prevalence of HIV and HCV. Debate also surrounds the safety of unpaid versus paid donors, source versus recovered plasma, and plasma-derived versus recombinant factor concentrates. However, Mr. O'Mahony added that given the reality that there are 300,000 people in the world who have hemophilia and who do not have access to *any* treatment, let alone plasma or recombinant products, the solution cannot be unequivocal—it is clear that globally, both segments of the debated dichotomies will be needed well into the future. While recombinant products may eventually meet the future needs of people with hemophilia, plasma-derived factor concentrates have had an excellent safety record for over 10 years. "The real issue is the provision of safe, efficacious replacement therapy in adequate amounts, with the assurance of availability," he stressed.

Traditionally, the concept of safety for hemophilia products has often been defined in terms of enveloped viruses, non-enveloped viruses, theoretical risks such as vCJD, and emerging risks such as West Nile, SARS, or the next agent. However, the concept has expanded to include risk of inhibitors, efficacy and recovery of products, availability of supply, and alternative sources in the event of emergencies. Cost, science, evidence, data, and reality are also critical factors to decision-making: "There is very little point in having a very safe, efficacious quality if it is not available or if a country can't afford it. Safety, supply, and affordability need to be seen as part of the same equation," Mr. O'Mahony stated. "We must decide not to make our decisions based on political considerations, national situations and unrealistic aspirations and timelines—these decisions should be based on data and reality, not sentiment."

Decisions affecting the lives of people with hemophilia must involve people with hemophilia, he said. In consultation with industry and the not-for-profit sector, the WHF has taken positions on EU directives and FDA guidelines, always with the viewpoint that such regulations have an impact not only in their regions but all around the world. In the end, he emphasized, the objective of all stakeholders is the same—to improve the quality of life for people with hemophilia and allow them to live life to their full potential. The WHF and hemophilia

organizations have a responsibility to develop the expertise and knowledge base to contribute effectively and rationally to the ongoing debate on safety and supply, he concluded.

What is Self-Sufficiency for Hemophilia?

Bruce Evatt, Hereditary Blood Disorders Division, Centers for Disease Control, U.S.A.

When self-sufficiency is viewed from a global perspective, the major issues determining risk for the majority of patients with hemophilia are product safety—which in the past pertained to infectious diseases—and the availability of supply. Both issues depend on the world in which the patient is situated, Dr. Evatt said. Historically, developed countries have had a tremendous need for fresh frozen plasma (FFP), which led to the organization of national hemophilia organizations with the objective of self-sufficiency. At that time, safety was a secondary consideration because the availability of FFP was critical.

The discovery of cryoprecipitate changed the scene in a number of ways. It led to the manufacture of concentrates and the pooling of tremendous amounts of plasma. With this came increased exposure to greater numbers of blood donors, increased frequency in transmitted infections, and increased concern over safety. The policy of self-sufficiency in the developed world grew out of this context, to arrest the emerging propensity to use plasma obtained from undesirable sources in the manufacturing process, Dr. Evatt said. Motivated by good intentions to prevent risk and improve the safety of products, particularly in light of the AIDS pandemic, the EU began to press hard on self-sufficiency. While blood safety is of primary importance in the developed world, however, Dr. Evatt noted it has weighty consequences in the developing world, where availability of supply remains the paramount issue.

In some countries since the mid-1980s, risks of infection have decreased with the improvement of blood product safety and the introduction of numerous types of viral-inactivation procedures for the three major viruses, HIV, HBV and HCV. People with hemophilia living in places such as the U.S., Europe, Canada, Australia, and New Zealand have adequate supplies of concentrates. However, developing countries face significant barriers,



tied to availability, costs, regulations, and basic manufacturing resources. "Supply remains the basic deficiency for most hemophilia patients in the developing parts of world, where the shortage of clotting factors remains the primary risk," he said. As reported to the WFH, only a small fraction of countries with an annual GNP of less than \$2,000 always have concentrates available; the vast majority only have concentrates available occasionally. A significant proportion of countries have rare or no availability, and are largely dependent on the availability of fresh frozen plasma or cryoprecipitate obtained from donations within their own country.

Volunteer blood donations the world over are driven by the need for red cells and platelets, but the supply of recovered plasma is almost never sufficient to supply the needs of hemophilia, Dr. Evatt said. In fact, in a survey, at least half of WFH member countries reported collecting less than 200,000 donations of blood for recovered plasma within their own countries—vastly insufficient.

Even with the best blood bank and transfusion practices put into place, Dr. Evatt said, the risk of disease transmission through these donations is considerable. Risk depends upon the prevalence of infections among donors. For patients with hemophilia, risk is also cumulative—with their repeated use of blood and plasma products over many years, risk adds up significantly. "But the theory of cumulative risk is not really understood by public health officials, who believe that their blood products are quite adequate and safe because they keep to best practices. Furthermore, under the guise of the need for self-sufficiency, infection risk is used to prohibit the importation foreign-made products—but this can be devastating," Dr. Evatt said.

A comparative study of Venezuela and the U.S. carried out by the CDC illustrated cumulative risk. While Caracas has outstanding blood collection and practices, the frequency and prevalence of HIV among the donations meant that after 10 years of treatment, people with hemophilia (PWH) there were at eight times higher risk for transfusion infection than PWH in the U.S. The study found that, despite following approved testing and inspection methods, risk is cumulative; with its HIV prevalence rates, PWH in Venezuela faced a 40% risk of transfusion infection after 60 years of treatment, compared to a 2% risk in the U.S. The prevalence numbers are even higher for HCV, Dr. Evatt noted.

"From a patient perspective, a policy of self-sufficiency is frequently a barrier to access to safe concentrates, especially when it is used to prohibit the importation of concentrates made from foreign plasma," he said. Yet there can be a higher risk of therapeutics when only local plasma or plasma precipitate is used; furthermore, he noted, it appears to have no direct benefit to a patient in light of current technologies and little association with the original reasoning behind self-sufficiency. Dr. Evatt concluded with some provocative questions: Has the concept really outlived its usefulness? Did good intentions mainly yield unfavourable results in many countries because these intentions were designed to aid one segment of the global population, namely the developed countries, without consideration of the impact on developing countries?

Self-Sufficiency: Evolution of an International Concept

Albert Farrugia, Blood and Tissue Services, Australian Commonwealth Therapeutic Goods Administration

The concept of self-sufficiency in blood supply emerged more than 30 years ago, when the World Health Organization grew concerned that some practices in the developed world (such as growing commercialization of the blood system) were taking place through the exploitation of blood donors in developing countries and at the expense of the development of domestic blood services. A meeting involving the League of Red Cross Societies resulted in the May 1975 resolution regarding "voluntary non-remunerated donation" and the emergence of the concept of self-sufficiency in terms of national needs, Dr. Farrugia explained.

The underlying concepts of self-sufficiency are to prevent the exploitation of third-world donors by commercial blood collection agencies, encourage development of blood services in developing countries, and address the high risk of transfusion transmissible markers in paid donor populations. Self-sufficiency offers safety from infectious agents, control over essential drugs, and encourages a local blood industry. However, Dr. Farrugia noted some shortcomings of self-sufficiency, such as measures that restrict access to blood products and the commercialization of traditionally voluntary sectors.

Citing an unscientific study of viral marker rates in different donor populations in 1996-98 (i.e.,



commercial and voluntary donors in the U.S. and voluntary donors in Europe), Dr. Farrugia maintained that there is no evidence that voluntary donors present greater safety or lower risk of transfusion transmissibility. "I believe that safety is not a function of whether you are self-sufficient or not, nor is it a function of whether donors are remunerated or not—it's a function of the whole system of blood collection, testing, manufacturing, and regulation."

The blood products industry is the most regulated one in the pharmaceutical sector and there are many measures and restrictions in place to provide a high level of assurance to manufacturers and regulators so that the mistakes of past will not be repeated, he added. There are clearly arguments against having a so-called self-sufficiency policy for national safety and supply of products, since in reality no blood service can generate sufficiency in all products. "With one or two debatable exceptions, for blood derivatives the world still relies on source plasma from the paid sector of the U.S.—this is undeniable, and denying access to products from this sector results in patients with hemophilia being denied sufficient therapy."

Dr. Farrugia commended a policy in Brazil to generate self-sufficient fractionation capacity within the country. Brazil has a current generating capacity of 250 tonnes of plasma annually, which it aims to increase to 400 tonnes annually. However, given Brazil's population of 170 million, its current FVIII consumption of 0.9 IU per capita can hardly be considered self-sufficiency in relation to modern hemophilia care, he said. He emphasized that "the principle of self-sufficiency does not mean that plasma must be fractionated by a domestic fractionation facility."

Dr. Farrugia pointed to data on self-sufficiency of FVIII in Japan, indicating that FVIII consumption is currently 1.54 IU per capita. Is that self-sufficiency? Similarly, if self-sufficiency means FVIII consumption of 1.19 IU per capita, the EU blood collection is vastly inadequate to meet demand, he noted. Yet, its 2002 blood directive allows for the prohibition or restriction of imports of blood and blood components. "I challenge European Union governments whether they are ready to provide recombinant FVIII to make up for the shortage. The goal of any blood policy is to achieve a safe and secure supply, and that sufficiency and quality has to go hand in hand. Safety cannot be achieved if we do not have sufficiency."

The fact is, economics determine treatment globally, with a clear relationship between the amount of blood available and the economic index of a country. In the vast number of countries in the developing world where economic issues are paramount, there is not enough donated blood. Furthermore, transfusion transmissibility of infections remains a large problem in domestic blood systems in places like Africa and India, despite having been erased in other parts of the world. Dr. Farrugia noted: "If you're making cryoprecipitate and also trying to achieve self-sufficiency in this kind of environment, you are basically condemning the hemophilia population to significant morbidity and mortality."

Safe or unsafe, he concluded, most of the world doesn't have enough blood and economic and political arguments should not be used to cloud the real issue at hand, getting blood products to the people who need them. Some countries in the developed world have an excess of plasma products, he noted, but why isn't this surplus used in other capacities where they are needed? Safety is not a function of altruism but rather of resources, Dr. Farrugia said, and the principle of self-sufficiency requires critical review.

Blood Safety and Sufficiency— The Efforts of the Global Collaboration for Blood Safety

Jay Epstein, Office of Blood Research and Review, FDA, U.S.A.

With its origins in the 1994 Paris AIDS Summit, the GCBS was established by the WHO in 2000 to address emerging issues in blood safety and find solutions to worldwide problems with safety and availability, including plasma and transfusion components. Dr. Epstein explained that the rationale behind the GCBS is to improve global blood safety by raising international awareness and developing strategies and guidance on issues of global concern, fostering collaborative governmental and non-governmental efforts, and suggesting effective, practical, and realistic mechanisms for progress. The GCBS aims to promote and strengthen international collaboration on the safety of blood products and transfusion practices by facilitating information gathering and exchange, and promoting the safety, adequacy, quality, and appropriate use of blood and blood products globally.



The GCBS seeks to facilitate progress on essential blood safety principles, such as to help establish national and regional blood programs, priorities for the prevention of transfusion-transmitted diseases (TTDs), and equitable access, safety, and non-discrimination principles regarding plasma and derivatives for donors as well as recipients. Dr. Epstein noted significant issues such as where and how plasma is collected, international trade in blood products, and bi-directional traceability of blood products. It is essential to develop an evidence base on blood product use, he said, to “cease flying by the seat of our pants as to what is the right amount to transfuse, when to transfuse, and what product to use.”

While there are many international fora for blood, the GCBS is the only forum designed as a venue for dialogue among a very diverse set of stakeholders—inter-governmental organizations, international NGOs, government institutions (i.e. regulators), international industry associations, agencies, and experts from both developed and developing countries working towards the common goal of global blood safety as equal collaborative partners. He noted the special relationship between the GCBS and the WHO is because of the close alignment between GCBS goals and objectives, and the WHO programs and priorities.

The essential function of GCBS is to find common ground for collaboration; therefore, GCBS makes non-binding, consensus proposals to its own participants. However, Dr. Epstein noted, “These proposals may also constitute a reference for guidelines, policies, or other actions of participating bodies and are seen potentially as models to be adopted around the world.”

Key recommendations have emerged at the past three annual plenary meetings. In 2000, the focus was on global goals, with recommendations for a policy formulation tool, risk-monitoring by national authorities, information gathering and sharing, continuing improvement within national blood transfusion services, and the crying need for coordination of efforts. In 2001, the focus turned to the need to develop guidelines for good policy practices, the value of a GCBS website as an international communication tool, the concept of developing an accreditation mechanism for blood transfusion services so that they could progress toward benchmark standards, and the development of an assessment model to determine how much product and what products a country needs. In 2002, recommendations focused on promoting

awareness of GCBS, addressing GCBS finances, and clarifying the tasks of the working groups (policy process, plasma issues, quality assessment, and assistance for development).

The working group on policy process is based on a concept that was largely driven by the impact of AIDS and the need for national health ministers to respond politically to issues of accountability for blood safety and availability. It focuses on the need to define principles of good policy-making analysis as well as principles of good manufacturing practices within the larger context of public health, and to develop a model for decision-making for blood products. It also works to promote enhanced commitment by policy-makers to support nationally coordinated blood transfusion services and good policy practices.

Some of the principles being developed by GCBS include the prioritization of resource allocation in the context of overall public health—a concept, Dr. Epstein explained, that aims to free individual countries to make decisions that are appropriate within the context of their needs and resources. The decision-making process must include the consideration of scientific evidence; use of risk assessment, risk/benefit analysis, and risk management tools; communication of risk to user populations; and international communication of the scientific, economic, and social basis of policy decisions.

Another working group focuses on the plasma issues in blood safety, which have historically been driven by global trade and their safety and economic implications, Dr. Epstein said. It focuses on developing factual information to promote safe practices in the collection, storage, and transport of plasma, and the preparation and distribution of plasma derivatives; providing guidance on national decision-making regarding alternative strategies for providing plasma derivatives (e.g. local fractionation, “toll” fractionation, importation), and promoting the transfer of technology and advances related to quality system management in plasma fractionation.

The third working group focuses on quality assessment and assistance for development. It is working to develop generic global minimum requirements for blood transfusion services for consideration by the WHO; guidelines to assist in the preparation of regional or national standards based on minimum requirements; assessment tools for blood needs; and mechanisms to facilitate



progress towards external assessment and accreditation through national or international accreditation organizations. Pilot testing of a needs assessment model has begun in Honduras, Argentina, and Brazil, Dr. Epstein reported. The next GCBS annual plenary meeting takes place in December 2003.

Plenary Discussion

A participant challenged the notion raised by Dr. Farrugia that safety is not a function of self-sufficiency or payment and invited more discussion on the role of the screening process and questionnaire as a safety mechanism. Questionnaires go beyond physical and scientific tests by examining for the possibility of eliminating behaviours that may be associated with risks, such as HIV and HCV in the past, or may pose future risks associated with new emerging viruses for which there are no tests or attenuation processes, he said.

Dr. Farrugia said that the biggest difficulty in defining safety and in trying to compare the benefits and risks of paid versus unpaid donations is that the populations are generally very different, for example, in terms of whether plasma is derived from whole blood, recovered blood, or plasmapheresis. He suggested that safety is more significantly a function of whether environments are well regulated, rather than whether donations are paid or unpaid. "It would be very good if the massive efforts which have yielded so much fruit in the voluntary blood donation systems of the developed world could result in comparable outcomes in source plasma donations compared to recovered plasma." Unfortunately, it has not happened and the reality is that access and sufficiency in plasma fractionation has entirely depended upon the source paid plasma collection in the U.S. As to the questionnaires, he stated that irrespective of the altruistic function, there is insufficient evidence that voluntary donors lie less frequently or have a greater propensity to tell the truth than donors in the source plasma paid sector.

Dr. Epstein expressed that donor questionnaires continue to serve an important function by limiting the infectious burden in the fractionation pool, acting as an added safeguard and tool for ensuring product safety. "The real issue and overriding concern globally is countries where there are unpaid plasma programs but they use transmissible

components for donation, and where the drive for plasma self-sufficiency creates unsafe transfusable components." He noted that developed countries have many additional controls for safety, such as the inventory quarantine and hold, NAT testing, qualified donor program, pathogen inactivation, etc. Studies in the U.S. have shown a higher incidence in the underlying population of unpaid donors, but when the safeguards are put into place, the result is an equally safe product. However, that safety is process dependent and requires vigilance in maintaining good manufacturing practices. "One has to look at the system as a whole, and you cannot divorce the question of paid versus unpaid donor without looking at the system in which the blood is collected and processed."



The Economics of Self-Sufficiency

Chair: Mark Skinner, National Hemophilia Foundation

Mr. Skinner introduced the session by explaining the importance of understanding the economics of self-sufficiency and the intricacies of the global plasma market. Before beginning the session, he polled participants:

Is it cost effective for more countries to develop their own fractionation capacity?

Yes: 25%

No Opinion: 12%

No: 63%

Trends in the Global Blood Products Market: WTO, EU Rules, and the Effect of Recombinant Products on World Supply

Jan Bult, President, Plasma Proteins Therapeutic Association (PPTA)

Noting that he was not able to “paint a very rosy picture” regarding trends in the global market, Mr. Bult commented that global supply and economic issues could be examined from multiple perspectives including those of patients, hospitals, physicians, politicians, insurers, and the general public. He said he would focus on the industry perspective, which is often omitted from the equation.

Mr. Bult presented a list of the broad range of plasma-derived and recombinant products currently being produced and distributed. That range is important because no single country or producer can manufacture the whole range of products. Instead, the majority of countries produce a selection of the products. There are three recombinant products currently available (rFVIIa, rFVIII, rFIX). The important question, he said, is what is the role of recombinant FVIII and how will it be used globally.

It is important to address the issue of safety, which underlies most concerns regarding treatment

products. After the weekend’s workshops and various scientific presentations, it seems clear that current plasma-derived products are safe if they are manufactured with strict adherence to quality standards and rules.

Mr. Bult stressed that it is not possible to attain absolute safety with recombinant products. There is a risk in all therapies and products that contain some human-derived proteins. What is necessary is to reduce the risks as much as possible, while remembering that supply shortages can also create serious crises.

In North America, 70% of the product used is recombinant. In the European Union, nearly 60% is recombinant, while Japan uses over 50% recombinant. It is critical to understand that both plasma-derived and recombinant products are safe.

Many people ask how fast we can transition to recombinant products, Mr. Bult noted. He cautioned that, in a world where only 30% of the hemophilia community receives any form of treatment, a step-by-step approach, which takes economic factors into consideration, is necessary. He stressed that product availability and accessibility is also a safety issue and predicted there would be the need for both therapies for the next several decades.

In terms of self-sufficiency issues, he stressed that no one objects to collecting more blood or plasma. However, transfusion issues are distinct from plasma issues. Mr. Bult quoted Jean Emmanuel of the WHO: “Blood is local; plasma is global.”

Mr. Bult observed that patients and physicians have the right to expect high quality, safe products. However, self-sufficiency principles create artificial barriers, and are often driven by financial considerations from local interests. Moreover, they can lead to monopoly situations that result in high prices and discourage research and innovation. It’s important to recognize that there are unlimited needs but limited resources that necessitate making rational economic decisions.

Different actors have different approaches to decision-making, Mr. Bult stressed. Regulators must make decisions independently of cost issues, while reimbursement authorities take the opposite perspective. Unfortunately, the patient is stuck in the middle. It is often necessary to weigh the effect of expenditures on benefits. A relatively small investment in products and treatment can lead to a



significant improvement in patient condition, he said, but further marginal benefits come at a much higher cost.

Mr. Bult described the industry interest in the current scenario, stressing the need for a system that is so robust that it can survive crises like West Nile, extreme shortages, or emerging pathogens. Beyond quality issues, ethical issues must be considered.

To understand the perspective of the industry today, he said, one must be careful not to make comparisons with “Big Pharma.” Source material costs in the plasma proteins industry accounts for 65% of total costs, compared to only 25% for Big Pharma. The substantially higher source material costs mean that only half as much can be spent on research and development. Profitability is also much lower, hovering between 5% and 10%.

The industry functions within the most stringent regulatory requirements – the situation is complicated by the lack of a level playing field when competing with companies that receive government incentives like tax exemptions. It is further complicated by the lack of alignment between regulatory requirements and reimbursement practices. Although there is a global trend toward regulatory harmonization, the plasma proteins industry has been exempted for the International Conference on Harmonization process.

The industry has the responsibility to provide a safe and secure supply of treatment products, he said. Any transmission of a virus is unacceptable. It is necessary for all producers to ensure safe products, while regulators are obligated to verify the information presented and ensure that the same standards are set for all players. Physicians, said Mr. Bult, must make rational, not political- decisions about treatment modes, while patients must be critical and questioning.

There are artificial barriers to market access:

- In Belgium, in 1994-95, it was necessary for importing companies to prove their product was “superior and indispensable” before it would be admitted. The industry challenged that regulation and won after an eight-year court battle.
- In Denmark, companies were required to collect all plasma through

one organization and were then told what they could charge for products. Those barriers were legally challenged and struck down.

- In France, the marketing authority for companies using French plasma is five years, while for other countries it is only two years.
- In Taiwan, companies were told there would be preferential use for products made with local plasma.

Mr. Bult explained the new blood law in Japan in detail. It consists of labelling requirements, demand, and supply plans. This new law was developed in response to the enormous amount of pain arising out of the experiences of the 1980s and the more recent shortages in recombinant products. However, it will result in the limitation of imports, the obstruction of free markets for products, and reduced competition. Industry views this as a violation of the World Trade Organization and is considering a legal challenge.

The law also contains a requirement that all products be labelled as either *kenketsu* (in compliance with International Red Cross definitions, voluntary plasma donations, and requirements, or collected in a country with its own definition) or *hikenketsu* (which simply means “not *kenketsu*” or not voluntary).

Even the Japanese Ministry concedes that all products are safe and has pledged to inform physicians and patients of that fact, said Mr. Bult. However, the designation of two different types of products creates feelings of insecurity. Research indicates that 40% of patients say they would prefer *kenketsu* products, which are collected in Japan from Japanese donors, while 40% would depend on their physicians’ choices. Nearly 60% say they would feel insecure using products that were labelled as *hikenketsu*, even though there is no evidence that these products are less safe.

The demand and supply plan requires all manufacturers to provide forecasts of their production and anticipated import volume to Japan each year. Mr. Bult said this would be a serious problem in countries like the U.S.A., since it would be an anti-trust violation. The ministry will measure the forecasted production against the expected



demand. When the ministry notes a discrepancy, it will request that companies adjust their import volumes accordingly. If companies do not or cannot comply, operations can be ceased. This raises the possibility that, in times of global shortage, the ministry could demand that producers supply Japan first or risk being denied access to Japanese markets altogether. If implemented, the resulting import restrictions create a strong case for a WTO violation.

Domestic and Contract Plasma Fractionation Programs: Economic Aspects and Impacts on Local Hemophilia Care

Thierry Burnouf, Director, Human Plasma Product Services

Dr. Burnouf examined whether or not domestic or contract fractionation are safe, viable, efficient ways to provide good products and improve the access to high quality care for hemophilia populations, particularly in the developing world. A number of factors play roles in the cost of plasma fractionation:

- The costs of collection and testing of starting material (plasma)
- The pool size for plasma and end products
- The portfolio of products produced, and batch size
- The yield that the particular manufacturing process allows
- Technology licensing costs

All of these factors have an impact on whether domestic or contract fractionation is a more sensible option in a particular situation. In both contract and domestic fractionation, Dr. Burnouf noted, the cost of plasma plays a key role and is about 45% of total production costs.

A number of countries, including Norway, Poland, Luxembourg, Greece, Canada, Hong Kong, Malaysia, New Zealand, Taiwan, Morocco, Tunisia, and Brazil have contract fractionation agreements. Dr. Burnouf calculated that contract fractionators process approximately 700 thousand litres of plasma annually, yielding 105 million IU of FVIII. At treatment levels of 50,000 IU per patient per year, this produces enough product to treat nearly 2,100 adult hemophilia A patients annually.

The American and Australian Red Cross also

conduct important contract fractionation programs. Together they produce 255 million IU of FVIII annually, which is enough to treat 5,100 adult patients.

Dr. Burnouf outlined the specific cost factors that must be considered with contract fractionation programs:

- Collection and testing of plasma for fractionation, and whether recovered or apheresis plasma is used.
- Storage and shipment, which can range between \$1 and \$7 per litre (all prices stated in US dollars).
- The costs of licensing and clinical trials.
- Distribution and marketing costs.
- The contract fractionation cost, which can be calculated as either the price per litre of plasma fractionated or the price per gram or IU of products returned.

Dr. Burnouf explained the factors affecting the charge per litre of plasma fractionated, which include the following:

- The plasma/product pool size.
- Additional testing and audits (e.g. NAT) that must be conducted to conform to particular regulatory regimes.
- Specific requirements (such as smaller vial sizes).
- Lower overall productivity due to factors such as batch segregation, smaller batch size, or smaller portfolios.
- Whether intermediate and some end products can be sold by the fractionator.
- Commercial agreements.

Dr. Burnouf outlined the criteria he used in his costing model. The model was based on the production of four products: FVIII, FIX, IGG and albumin. Plasma cost allocation will depend on collection mode, he said, but ranges from \$.04 to \$.25 per unit. Fractionation costs range between \$.19 and \$.45 per unit. Therefore, he said, the total cost of contract fractionation for FVIII ranges from \$.20/IU, best-case scenario, to \$.69/IU, worst-case scenario.

Specific examples of the impact of contract fractionation on hemophilia care in a number of countries were provided. In Brazil, for example, the products yielded will be 30% cheaper than imported products. In Malaysia, they will save 3 million Euros annually. In Morocco, the FVIII, yielded through their contract with France, costs \$.31/IU,



as opposed to \$.73/IU for imported products. Estonia, on the other hand, has cancelled its fractionation contract because it was yielding too much albumin.

Next, Dr. Burnoff outlined the specific costs entailed in domestic fractionation:

- Facility costs, including engineering, land buildings and equipment.
- Training and recruitment.
- Qualification and validation processes.
- Regulatory processes and clinical studies.
- Technology transfer and licensing costs.

Using the same set of assumptions for a costing model and factoring in a range of facility costs, Dr. Burnouf determined the cost of domestic fractionation for FVIII would range between \$.12 and \$.62 per IU. Some of the factors that could affect the final cost included batch size, yield, and varying licensing charges.

The crucial element in choosing between contract and domestic fractionation, he concluded, is the plasma price and the current availability of source material. Product portfolio is also important, since the cost of FVIII is linked to the demand for other products. Yield and batch size are also important, as are construction and local regulatory costs. Other decision-making elements, he noted, include financial and regulatory barriers, particularly since the plasma products industry is the most heavily regulated.

Partnerships with established fractionators can be very effective. In some cases, countries enter into contract fractionation agreements, then gradually develop their own domestic programs. He reminded participants there continues to be a significant difference between the technology necessary for the production of standard drugs and biopharmaceuticals.

Plenary Discussion

Following the presentations, Mr. Skinner posed several questions to participants.

Is it cost effective (economical) for more countries to develop their own fractionation?

Yes: 28%
Don't Know: 8%
No: 65%

What is the most economical course for a country to pursue if it desires to provide clotting factor concentrates for its population?

(Developing Countries Only)

Contract Fractionation: 41%
Develop Domestic Fractionation: 7%
Combination of Both: 52%

(All Participants)

Contract Fractionation: 54%
Develop Domestic Fractionation: 2%
Combination of Both: 44%

Would you be willing to pool plasma with another nation if it improved the viability of contract fractionation?

(Developing Countries Only)

Yes: 48%
No Opinion: 8%
No: 43%

(All Participants)

Yes: 48%
No Opinion: 7%
No: 44%



Self-Sufficiency and Fractionation in Emerging Markets

Chair: Alok Srivastava, Christian Medical College, India

How Are the Issues Defined?

Alok Srivastava, Christian Medical College, India

Only 26 countries out of over 190 worldwide are classified as developed economies by the World Bank, said Dr. Srivastava. These consist of Canada and the U.S., and about 25 countries in Western Europe, Japan, Australia, and New Zealand, where per capita GDP is over \$20,000. More than 150 countries are considered developing or emerging economies, where average income per capita falls between \$500 and \$6,000 with more than half the world's nations at under \$2,000 per capita – less than one tenth the per capita income of developed economies. Apart from major economic variation within this group, there are unquantifiable differences in their approaches to health and health care that affect the care of people with chronic diseases.

With pictures of people with hemophilia from different parts of world, Dr. Srivastava showed the great contrast in quality of life between people in developed and developing countries. Citing a 2001 WFH survey, Dr. Srivastava stated that, regardless of economic status, there is a direct correlation in the life expectancy of people with hemophilia and the number of hemophilia treatment centres in their country. There is also a strong correlation between musculo-skeletal function and the use of factor concentrates. A survey of patients in Sweden treated with different doses of factor and different intervals of care shows that the use of vast and large amounts of factor can almost abolish musculo-skeletal dysfunction in hemophilia.

In 2000, people living in the developed world and representing about 20% of the world population, consumed more than 80% of the world's plasma-derived factor concentrates. With the remaining 20%

divided among the rest of the world population, the ability to use products effectively is severely constrained, Dr. Srivastava said. About 80% of the 400,000 people with hemophilia in the world live in developing countries. Providing a minimum of 10,000 IU per PWH annually would require about 3.2 billion units of factor concentrates. This would provide 0.6 IU per capita factor concentrate but in reality this would be higher, as only about 30% of PWH in developing countries have been identified.

In 2000, the total factor concentrate production in the world was 3.7 billion IU, representing 2.1 billion IU plasma-derived and 1.6 billion IU recombinant. Dr. Srivastava said the notion of plasma self-sufficiency raises a number of important issues: Can 20% of the world supply enough plasma for the rest of the world? Even if this is possible, can it be done at costs that are affordable in developing countries? "With real and imagined threats to plasma-derived products, the production process keeps changing, and with each change, the cost of production keeps going up. Can emerging economies cope with these changing costs?" As plasma is needed for many uses other than factor concentrates, a crucial issue is whether there is a need for local self-sufficiency for those indications as well. "Self-sufficiency also needs to be taken in context of political and economic realities," he said. Apart from supply, the other major issue is whether adequate safety can be achieved. Can the quality of blood transfusion services be improved? Can regulatory standards be developed and implemented in these countries?

Issues also abound from the industry perspective. Can those industries looking at the global market provide factor concentrates to meet these needs at costs affordable in developing countries, and will these prices be viable when the product is manufactured under the regulatory requirements of the developed countries? If this is not possible, then is local fractionation a must? Furthermore, will governments actually invest and subsidize these efforts as a public service?

With regard to resources, Dr. Srivastava asked if it was a question of lack of resources in developing countries, or whether it was also an issue of skewed distribution of what's available. Data from the United Nations showed that military spending in developing countries outpaces health funding, he noted. In 1999, industrialized economies spent more than 5% of their GDP on health expenditures amounting to >\$1000 per capita. Developing economies, however, spent about 3% on health



which translates to <\$10 per capita. In the same year, industrialized economies spent 1% to 3% of GDP on military expenditures, while developing economies spent 3% to 7% of their GDP on military expenditures.

If self-sufficiency is to be implemented, there are different models, Dr. Srivastava said. While large parts of the developing world, including Africa and South Asia, continue to use wet plasma/cryoprecipitate for factor replacement, Thailand and Cuba have established facilities for production of lyophilized heat-inactivated cryoprecipitate. Plasma is fractionated locally in South Africa and China, while other countries, such as Malaysia, use contract fractionation. Brazil and Argentina import significant quantities of plasma-derived concentrate. Different models will suit the needs and possibilities in different countries. "The reality of the world dictates that there will be different standards in donor selection, testing of source plasma (i.e. NAT testing), and purity after fractionation," Dr. Srivastava concluded.

Choosing Between the Options: Brazil

Luiz Amorim, HEMORIO, Brazil

Dr. Amorim began with a quick summary of this largest South American country. Brazil is an emerging economy with a population of around 180 million people, GDP of US\$390 billion, and annual per capita income of US\$2,200. The Brazilian health system offers universal access, free of direct charges. The Brazilian Blood Program is run by the National Health Vigilance Agency (ANVISA), and oversees transfusion medicine policies and regulations, a network of donor centres and transfusion services, the plasma fractionation program, and hemophilia care.

In Brazil, it is explicitly forbidden to sell blood, blood components, and blood derivatives, Dr. Amorim said. Blood donations are non-remunerated, altruistic, and anonymous. Federal regulations apply to all activities related to transfusion medicine, with inspection by health authorities performed once a year. A number of mandatory tests are performed on blood donations, including Anti-HCV and Anti-HBC. It is expected that NAT testing for HIV and HCV will be implemented by February 2004. Among the main objectives are self-sufficiency in plasma derivatives

and comprehensive hemophilia care for PWH. The prevalence of viral markers in blood donors dropped from 12.5% in 1998 to 7.3% in 2002, which Dr. Amorim acknowledged remains very high.

Nearly 95% of blood donations are fractionated at least into plasma and red blood cell concentrates. Platelet concentrates are prepared from 30% of donations. Apheresis is performed only for platelet collection; plasmapheresis is not performed. A small fractionation centre is currently producing albumin (30,000 litres per year). Dr. Amorim explained that Hemophilia A is treated with cryoprecipitate, with close to 15% treated with locally produced low purity FVIII. Hemophilia B is treated with fresh frozen plasma or prothrombin complex, and von Willebrand disease is treated with cryoprecipitate.

Brazil has seen major changes over the last 10 years. In 1994, the Health Ministry began to regularly import FVIII, FIX, and prothrombin complex. National guidelines for hemophilia treatment were implemented in 1995. A national registry of PWH was established in 1998. From 1998 on, there was the progressive increase of imported coagulation factors and regular importation of activated prothrombin complex for patients with inhibitors. In 2001, Brazil began small-scale importation of recombinant FVII. There are more than 7,600 people in the national PWH registry. Since 1998, the Brazilian Health Ministry has imported 30,000 IU of FVIII or factor IX per PWH per year, Dr. Amorim reported.

National guidelines for PWH in Brazil include the following:

- Proposed doses for each type of bleeding or surgery;
- No primary prophylaxis;
- Inhibitors treated by FEIBA or prothrombin complex;
- No protocols of immune tolerance; and
- Products supplied to regional blood transfusion centres that distribute them to hospitals and clinics.

In 2002, a federal regulation stated that cryoprecipitate cannot be used for hemophilia or von Willebrand treatment, and new regulations were enacted concerning the importation of coagulation factors.

Brazil has chosen to strive for self-sufficiency in plasma derivatives, said Dr. Amorim. This began with contract fractionation and involves the



construction of a plasma fractionation centre with a capacity of 500,000 litres annually. Dr. Amorim explained that the decisions were made based on plasma use in the country. In 2001, Brazil had collected nearly 3.1 million units. About 9% were discarded due to viral markers, and another 5% to other losses. Brazil currently has at least 150,000 litres of plasma available for fractionation per year for producing albumin, IVIG, FVIII, FIX, and prothrombin complex.

Standards for treatment for PWH in Brazil are improving. Although self-sufficiency for FVIII is still far off, local plasma fractionation is considered strategic for the country. Dr. Amorim reported that a state-owned, not-for-profit plasma fractionation centre would be established soon, with construction beginning in 2004. However, self-sufficiency should not be seen as a barrier for importing blood products. He added that Brazil intends to have local production and self-sufficiency in 10 to 20 years, and will stop importation only if needed.

Choosing Between the Options: South Africa

Duncan Armstrong, Natal BioProducts Institute

Dr. Armstrong discussed the South African experience. Production of plasma products is based on non-voluntary remunerated donors for whole blood and plasmapheresis. Its goal is to promote self-sufficiency in plasma products in South Africa. It takes into account the benefits and the inherent safety of a gift and optimizes the use of the blood donation gift. Manufacturing options are chosen in line with the evolution of available products and technology; some of the technologies have come via support from the European Plasma Fractionation Association. Working within the confines of the South African environment, Dr. Armstrong said, the key issues are affordability, accessibility, and sustainability.

The South African national blood policy includes the aim of plasma supply to meet self-sufficiency objectives. Blood transfusion products and fractionation are regulated and controlled by the Department of Health. The South African National Blood Service diffuses more than half a million units of blood concentrates. All donations are viral-marker screened and component preparation is made from more than 95% of the donations collected.

Until 1965, South Africa used fresh frozen plasma. In 1968, freeze-dried cryoprecipitate and home therapy were introduced. Component therapy was then introduced via best transfusion practice, to increase the availability of the plasma. The development of heparin-purified SD product offered greater access to PWH in rural areas through its storage capacity at room temperature. Small pool heat-inactivated cryoprecipitate was also introduced. FIX was used until 1990, when freeze-dried prothombin complex concentrate was introduced. In 1989, South Africa began producing its own FIX.

Self-sufficiency, according to the WHO guidelines, has motivated blood services. From 1999 to 2002, fresh frozen plasma volumes increased from 50,000 to 110,000 litres. The method of freezing improved as did the quality of FFP for both therapeutic and fractionation use. Dr. Armstrong emphasized that high quality FFP is essential; therefore, it is occasionally supplemented with imported cryoprecipitate from voluntary non-remunerated donors.

Plasma safety is dependent on the source of the blood and processes like donor selection, testing, cGMP, and compliance with regulations. "You build in safety; you don't just test for it," Dr. Armstrong said. At later stages, FVIII is reviewed for clinical efficacy, viral safety, and inhibitors. Low inhibitor levels are important because of limited access to treatment for inhibitors. Products are also subject to pharmacovigilance.

There are more than 44 million people in South Africa and only 1,910 PWH identified — a substantially lower figure than believed to be true. The current treatment level for FVIII is 0.67 IU per capita. "In terms of hemophilia care, we have very good on-demand therapy, but very limited primary and secondary prophylaxis," Dr. Armstrong said. Supported by the WFH, the South African Hemophilia Society has gained acceptance of a comprehensive hemophilia care model for South Africa, culminating in a national policy in 2000, underpinned by a risk management protocol, nine comprehensive hemophilia care centres with a multi-disciplinary team and a dedicated hemophilia nurse, and two regional treatment centres.

Hemophilia management has devolved to the provincial level, with a formal referral procedure accessible to all PWH. A Hemophilia Nurses Committee has been established to promote optimum care through activities to expand nurse



member knowledge and a hemophilia outreach protocol. Educational and support programs have been extended to the South African community. A Hemophilia Outreach Program aims to ensure that all PWH receive adequate care and treatment. As can be seen by the numbers, Dr. Armstrong noted, South Africa faces a problem with identification of PWH. The outreach program also aims to educate healthcare professionals, PWH, and their caregivers with home therapy training, hemophilia nurse training, and information such as awareness programs and treatment guidelines.

Future challenges from a product perspective include double viral inactivation, high-purity products, and the possible introduction of recombinant products. Pitched against this are considerations of reduced yield and the risk-benefit of improved safety and increased cost. Furthermore, budgetary constraints are quite severe in healthcare because the focus is on primary health care, Dr. Armstrong said.

Alternative approaches include imported products, recombinant FVIII, and gene therapy. The financial impact of alternative products is quite complex because of the close interaction between transfusion and fractionation, Dr. Armstrong noted. Any loss in terms of revenue from plasma to fractionation will lead to an increase in red cell/platelet prices. Imported products would reduce the cost effectiveness of fractionation. This is a careful balance and is crucial when deciding whether to set up a fractionation centre.

Challenges that have an impact on patients include guarantees of continuity of product supply, long-term affordability (affected by fluctuating exchange rates), and international pricing.

The way forward for the NBI, he concluded, is to improve product design for hemophilia management, taking account of country constraints; identify appropriate options suitable for South Africa; continue to work closely with blood transfusion to ensure acceptable plasma quality and safety; and support initiatives to extend access to PWH in South Africa.

Choosing Between the Options: India

Urmish Chudgar, Advanced Transfusion Medicine and Research Foundation, India

The Transfusion Medicine and Research Foundation is a newly established NGO whose aim is to make India self-sufficient in blood products and plasma derivatives—a lofty goal, Dr. Chudgar conceded. Located in the state of Gujarat in western India, Ahmedabad is a city of 5 million people, a few hundred miles north of Bombay and about 200 miles southwest of Delhi. India occupies about 2% of the land in the world, yet is home to 16% of the world population. The region is densely populated and very geographically diverse, with hemophilia patients throughout. PWH with bleeds can travel hundreds of miles to get a transfusion. The delay and inadequate treatment often results in chronic arthropathy. Although PWH and their caregivers accept these circumstances, Dr. Chudgar said the conditions and attitude need to be changed.

Dr. Chudgar said that much needs to be done in establishing infrastructure and improving the number of doctors and hospital beds in both rural and urban populations. With a GDP of about US\$800 per capita and a miniscule health budget (0.6%) most medical needs are covered by the private sector. Health insurance other mechanisms of healthcare support covers less than 10% of the population and over 75% have to pay for care on their own.

There are about 10,000 registered hemophilia patients in India, but considering incidence brings the figure close to 60,000 PWH. Average life expectancy is under 30 years. There are 56 hemophilia centres and 12 comprehensive centres in India; however, Dr. Chudgar noted that diagnostic facilities and FVIII and FIX are not readily available in many states of India. Factor concentrates are supplied through the local chapter of the Hemophilia Federation (India). Even at minimum replacement levels of about 5,000 IU per year per PWH, the yearly average cost of treatment per patient is 150,000 rupees—three times the average household income. A large number of patients depend on cryoprecipitate, fresh plasma, and even fresh whole blood.

The aim of self-reliance for India involves three main issues: plasma safety, plasma fractionation



technology, and logistic and financial issues. Safe plasma is linked to plasma importation, plasmapheresis, and recovered plasma. Plasma imports are not affordable, Dr. Chudgar said, and therefore India has to generate its own plasma. Plasmapheresis is another option; however, a federal law states that any plasma-related activities done for commercial purposes where financial remuneration is involved is not allowed. There is ambiguity concerning plasmapheresis for plasma fractionation, and whether that will be allowed or not.

Recovered plasma is, in reality, India's only option, Dr. Chudgar said. However, the blood banks have been mired in bad press, blamed for the spread of AIDS, black marketing, profiteering, and exploiting blood donors. There are 1800 blood banks in India, which collect 5.5 million units of blood yearly. Faced with misinformation and an acute void of data, Transfusion Medicine and Research Foundation undertook a study of India's situation, based on 140 blood banks from all parts of the country. The majority of blood banks (69%) collected less than 10,000 units annually. Blood banks collecting from 10,000 to 25,000 units accounted for 24%, with only 7% collecting more than 25,000 units yearly. The study also found that 20% of the blood banks were collecting 350 ml of blood, rather than 450 ml of blood, which leads to a lower amount of recovered plasma.

Most of the blood banks depend on replacement donors, a practice probably unique to India, Dr. Chudgar said. "When somebody needs blood, they need to bring a donor along with them, to replace the unit of blood." However, he reported that replacement donors are more likely to lie and hide information in circumstances where relatives need blood urgently. "Ideally, replacement donors should be banned," he said, but the study showed that 87% of blood banks depend on replacement donors. Only 47% had componentization facilities and, while all blood banks had testing in place for HIV, HbsAg, and HCV, none had proper quality control and assessment systems.

In 1999, the foundation launched a pilot project, called the Prathama Blood Center. Based on 100% voluntary donations and 100% component preparations, the Prathama Center is managed by professionals trained in transfusion medicine. It collects about 50,000 units annually, with an automated and integrated system for tracking blood donors and products. Another feature is optimum storage capacity for managing epidemics or

shortages. Training and education is given at the post-graduate level, and a rigorous quality control and assessment system has been put in place.

The Transfusion Medicine and Research Foundation also provides support for setting up or upgrading transfusion centres. Its focus now is to duplicate the process across India. Between 20 and 30 centres are needed throughout India to meet the country's needs, Dr. Chudgar said. A centre is being built in Delhi, and negotiations are ongoing for upgrading centres in Bombay and Calcutta. "Being dependent on recovered plasma requires significant upgrading of the blood banks, which in turn leads to componentization of blood, and need for safe plasma for plasma fractionation," he said.

India previously had a fractionation centre, but it is no longer operational. Support is needed with plant design, viral inactivation, and engineering technologies. Many of the technologies come with heavy licenses because there is some doubt about the amount of safe plasma that can be collected, and the possibility that recombinant technology for making FVIII and FIX will become increasingly tempting and interesting.

Until India has FVIII or FIX or fractionation capacity, its options are to import plasma products, to develop products at blood banks, contract fractionation or set up plasma fractionation facilities. Contract fractionation is considered a first step towards a fractionation plant. About 20,000 litres of plasma have been collected yearly from the Prathama Center, a figure that should rise as the model is replicated across the country, Dr. Chudgar said.

Choosing Between The Options: China

Dr. Srivastava explained that Dr. Qian Kai Cheng of the Shanghai Blood Center had prepared a presentation on the plasma fractionation process in China, but was unexpectedly unable to attend the forum. Dr. Srivastava presented a summary based on his paper.

China has a population of 1.26 billion people; its GDP per capita is US\$850, and health expenditure per capita is about US\$45. Fractionation in China began as early as the 1950s as a traditional method to prepare plasma for clinical applications. In the 1970s, large portions of plasma were fractionated



into albumin which, although more costly and time-consuming to prepare, is much more stable than fresh plasma. In the 1970s, the plasma fractionation business grew rapidly, with the motivating force being financial gain, according to Dr. Cheng, who wrote in his paper: "Due to higher profitability of albumin in market, overwhelming numbers of plasma centres appeared over all China like bamboo shoots after spring rain."

In the late 1980s, the Chinese Ministry of Health mandated a new plasma fractionation method, the Low-Temperature Alcohol Method. The early 1990s saw an outbreak of HIV and viral hepatitis in parts of China, which resulted in the shutting down of many plasmapheresis units. A landmark law was passed in 1998, stating that plasma centres could no longer use recovered plasma, only source plasma collected from paid donations. It also mandated automated source plasmapheresis.

The Ministry of Health also established the "one-to-one" rule, where one plasma centre can only be contracted with one fractionator; the plasma centre can no longer supply its source plasma freely. The standard set for each plasma centre is a minimum of 10 automated devices, processing at least 10,000 litres annually, in order to meet the goals set for plasma collection. Donors are paid US\$10 per donation of 560 ml. Potential donors are rejected if they have a tattoo or body piercing, are homosexual, or, Dr. Srivastava observed with interest, if they have received growth factors. The required tests for plasma (HIV, HCV, HbsAg, etc.) appear to be carried out by the plasma centre, then repeated by the fractionator, Dr. Srivastava commented.

On paper, he concluded, the Chinese model using paid donations for plasma fractionation seems to be an amazing model that is unique among developing countries.

Plenary Discussion

Dr. Srivastava polled industry participants on the following question:

Can those in industry hoping to supply to the global market provide for the needs of the developing world and emerging economies in a sustained manner? (Regulators only)

Yes: 44%
No opinion: 25%
No: 31%

Dr. Srivastava then asked those who had responded with a yes opinion (44%) to answer the following question:

Can you supply at a cost likely to be affordable to developing countries (around 20 cents/unit)?

Yes: 38%
No opinion: 31%
No: 31%

Mr. Page noted that, according to Mr. Bult, there is a very low profit margin for commercial fractionators, about 5 to 10%. However, he suggested that comparing the price per FVIII unit in the U.S. to the estimated cost presented by Dr. Burnouf showed a fairly large discrepancy, an apparent gap of 50 to 100%. Dr. Srivastava agreed that plasma-derived concentrates can sell for from 10 to 60 cents per unit, but vary between high- and low-quality purity, which may explain the gap. A participant said it is important to consider Dr. Burnouf's presentation as a model, where certain assumptions are being made, but cannot be construed as the reality. "True life is that industry has to manufacture and produce products under very different conditions," he said. There can be many important company differences, such as the number of products it manufactures. Cost allocation is a key factor. The audience member pointed to the "attack" on albumin, which has drastically reduced its use and prices. The true answer can only come when you have a full picture of all products and can make a proper assessment, he said.

Dr. Burnouf added that one must acknowledge that fractionators may have other factors that affect price, such as distribution costs, etc.

Discussion focused on the meaning of self-sufficiency in FVIII treatment, in varying contexts of usage, demand and supply. Dr. Srivastava asked: What is appropriate therapy in this changing paradigm? The hemophilia community is still grappling with the question of optimum treatment.

Dr. Evatt replied that the answer really depends on what individual ministries of health identify as an appropriate goal—self-sufficiency or adequate care. "My problem with the concept of self-sufficiency as a kind of holy grail is that it is really damaging the care of patients with hemophilia in many countries, because ministries of health want to fulfill these recommendations for self-sufficiency as the overriding goal, at the cost of really adequate care



for patients. It's a misunderstanding of what's important for those populations."

Mr. O'Mahony said adequate care is impossible to define. "But if you go from 0.5 to 1, and then 1 to 2 units per capita, you get a fivefold increase in survival. As you go beyond 2, you get more functional independence, and at 4, 5, or 6 units per capita, you start getting joint integrity. In every country that the WFH goes into, we try to look where they are and take the next step. You can't go from 0 to 6, but you can go from 0.5 to 1, and take things in sequence."



Emerging Safety and Supply Issues

Chair: Bill Mindell, Canadian Hemophilia Society

Challenges to the Bleeding Disorders Community

Mark W. Skinner, National Hemophilia Foundation

Mr. Skinner gave his presentation from a consumer perspective, attempting to examine what we should be thinking about emerging pathogens and what they mean to the global consumer community.

All of us know, he said, that there is a tripartite “unholy alliance” between the three components as they relate to hemophilia treatment products: safety, supply, and affordability. The global patient community is “only too aware” of what happens if you ignore safety, but it’s also apparent that if the focus is solely on safety, treatment products become too expensive to be practical. It is necessary to figure out how to keep all three elements in balance and still meet everyone’s goals.

Safety, Mr. Skinner said, will always be a primary concern for the community. We do not know what the next threat could be—a threat to the blood supply from a virus that is travelling around the world or a man-made issue, such as a bio-terrorism event. Consumers, he stressed, have a very important role in maintaining vigilance.

He outlined the historical evolution of the U.S. perspective on “zero tolerance.” The concept is really unattainable, even indefinable, he conceded. A better definition is constant and continued vigilance, seeking answers and continuous probing. Zero tolerance really speaks to the issue of what consumers are willing to accept, while recognizing the importance of their role in the process. The ultimate question is whether the goal of zero tolerance is at odds with providing a safe and accessible blood supply.

The complexities of the supply issue are becoming better understood, Mr. Skinner said. In the developed world, a major shortage of recombinant products – which are viewed as luxuries in most parts of the world – has already been experienced.

That, in turn, prompted a worldwide shortage of plasma products as they were diverted back to developed countries. Even recent events, like the case of HIV transmission in New Zealand, can cause local shortages. “In our zeal for advanced safety, if we don’t make some compromises, we’re all in jeopardy of having no product to treat with,” he said. The concern about adequate supply is shared between the developed and developing worlds.

Affordability is also a shared concern, Mr. Skinner said, because every incremental increase in the cost of products due to an additional safety measure makes treatment products more unaffordable for some. In turn, reimbursement mechanisms cannot keep pace with product development.

Mr. Skinner flagged several likely future challenges. It is necessary, he said, for consumers, producers, regulators, and government to share responsibility for blood safety, and to recognize the mutual co-dependence of all parties in this market. There must be recognition that there is a finite patient population, a limited capacity for supply and production worldwide, and limited capability for regulators to oversee products adequately due to time and financial constraints.

It is time to try to develop new collaborations, he suggested. There has been much successful collaboration at the regional and local levels. It may now be appropriate to expand those collaborations to a global level. There are still many countries around the world where effective two-way dialogue still does not occur, he said, but it has become generally accepted that consumers must be heard, as well as informed. Taking a more global perspective would enhance the ability to move products/components around the world in response to regional crises.

By examining global experiences it might be possible to look at new products and research rare bleeding disorders that don’t have large enough bases in individual countries. Now that it is well established that consumers have a right to be at the table and participate in decision-making, one of the major challenges is the need to harmonize regulatory requirements. There might be some difficulties with global harmonization, he said, noting the difficulty in bringing together divergent standards while trying to maintain the production of a wide range of different products. It is also important for the patient community to ask if harmonization will make products more or less accessible.



Mr. Skinner questioned whether it's possible to use an "emerging risk-decision matrix" to assist in orderly decision-making during times of crisis. He also asked if using marker viruses for verification and validation would be strong enough measures to maintain consumer confidence.

There is a shifting balance, he said, that is more complicated than risk/benefit. It arises out of the understanding that safety is also a supply issue. While it's important the blood supply and treatment products be as safe as possible, it's also critical that consumers don't demand excessive tests and procedures with only marginal value because there is a balance to be maintained between cost and safety/accessibility.

The consumer community has responsibilities that go hand-in-hand with its acceptance as partners in the decision-making process, he concluded. It's not acceptable to ask for everything possible; it's necessary to settle for everything that is practicable. Being included in the discussion process obligates consumers to practice "due diligence." Ultimately, he said, consumers are the guardians of the blood supply—"canaries in the mineshaft." While it's not what consumers want to be, he said, it has firmly established that they have a need and a right to a place at the decision-making table.

Update on vCJD

Bruce Evatt, Hereditary Blood Disorders Division, Centers for Disease Control, U.S.A

Dr. Evatt noted that understanding of vCJD has matured quite a bit. It's worthwhile reviewing some of the basic elements of "Mad Cow" disease to better understand where we stand. Typically, there were two agents to be considered, CJD and vCJD. Both created major disruptions in the plasma derivatives markets and in the availability of supply.

With classic CJD, he explained, it was believed that transmissible spongiform encephalopathy (TSE) infectivity could be present in blood and could possibly be present in plasma. Initial experiments showed that fractionation procedures with spiked samples could result in the presence of infective agents with the various coagulation factors, which caused a great deal of concern. However, when CJD was examined in a number of different clinical situations, it was determined that no patients with

hemophilia were found to have classic CJD. More importantly, patients that died with CNS problems in Canada and the U.S.A. were examined for evidence of prion material, but none was found. As more and more data accumulated, investigators came to the conclusion that classic CJD presented little or no risk of being transmitted through plasma or plasma products.

Of more concern, Dr. Evatt explained, was the occurrence of bovine spongiform encephalopathy (BSE), which is a human-created epidemic in cattle that ended up being transmitted primarily in the United Kingdom, but also in large parts of Europe and Asia, through the export of ruminant-contaminated feeds. This created the concern that the agent could be transmitted in blood or blood products, particularly because it appeared to be a more infectious disease, due to the high levels of infectivity, and because of its ability to jump species.

At the peak of the epidemic in cattle, there were more than 35,000 cases of BSE in the U.K., while the rest of Europe and Japan saw cases in the hundreds. The occurrence of new variant CJD (vCJD) began in humans at the tail end of the bovine epidemic and was quite different from the usual presentation of CJD. Its distinctive clinical features included the following:

- Young onset ages
- Early psychiatric symptoms
- Prominent ataxia
- The absence of periodic EKG activity
- Comparatively long illness
- Distinct florid or "daisy" amyloid plaque formation in the brain

The epidemic started in the U.K. and cases began to appear in other countries. Currently, there are about 137 cases reported worldwide, but it appears not to have spread to the huge numbers of patients originally feared.

More importantly, he said, published animal studies suggested that vCJD could be transmitted by transfusions, which was a major concern because many vCJD patients were later found to have donated blood. More recently, some fears have been allayed because studies and methods have been developed to test for prion material within plasma. In addition, a number of studies were conducted that have determined current methods for FVIII preparation remove 3 to 6 logs of vCJD, while FIX preparation methods clear 7 logs.



By 2002, it seemed clear that eating contaminated tissue predominantly transmitted vCJD. The epidemic is expected to peak in all of the affected countries within one to three years, with the greatest risk of vCJD remaining in the U.K. While it is still widely accepted that it's possible to transmit vCJD through blood transfusions, the probability of transmission is thought to be extremely small with plasma derivatives.

Extensive searches for human transmission of these agents by blood transfusion or plasma derivatives have not revealed any cases of infections, Dr. Evatt said. In the U.K., studies were conducted on patients with vCJD. Within the study group, eight patients had received transfusions, but none from donors who had been identified with CJD or vCJD. In a U.K. study of donation history, the blood donations of 14 vCJD patients were traced to 22 recipients, none of whom appear to have developed CJD or vCJD to date.

It is possible, Dr. Evatt said, for blood donations in countries with BSE and vCJD to contain low levels of the prion agent. However, animal studies support a consensus that fractionation processes for plasma derivatives remove infectivity. While continued vigilance and active surveillance are necessary, he concluded, the lack of transmission evidence to date suggests that vCJD is of less concern than some of the new emerging agents.

Safety Aspects of Locally Made Small Pool Hemophilia Treatment Products (Cryoprecipitate)

Albert Farrugia, Blood Safety Advisor, World Federation of Hemophilia

Although there is the sense in developed countries that cryoprecipitate is a less-than-ideal treatment modality, said Dr. Farrugia, it is important to remember that it was the primary way in which therapeutic hemophilia treatment became mainstream. More importantly, it continues to be a significant product, particularly in the developing world.

Nowadays, cryoprecipitate can be made more accessible, convenient, and stable by freeze-drying. There are several features affecting the quality of cryoprecipitate, including the need to optimize FVIII yield, minimize the fibrinogen and general

protein content, and create products that are presented in the most convenient way possible.

FVIII is known as an unstable protein, and in order to preserve it optimally, plasma must be frozen as soon as possible. Plasma that is frozen six hours after collection yields significantly more FVIII than that frozen after 18 hours. If plasma is allowed to warm up, then refrozen, FVIII yield does not change, but fibrinogen levels go up. All of these scientific reflections have resonance with regulators, Dr. Farrugia said.

Cryoprecipitate is a fairly crude product, which would not meet the same criteria for high purity, potency, and solubility as high-purity concentrates, he said. However, he stressed, it is a fairly safe product. It will never be possible to characterize the product through representative batch samples and label a vial of freeze-dried cryo for potency. It is also not easy to apply viral reduction techniques because these technologies are not easily adapted to blood centres and the product's low purity prevents heat inactivation. This essentially means that cryoprecipitate can never be made as safe as FVIII concentrates.

Dr. Farrugia presented studies determining the theoretical projections of the risk of persons with hemophilia contracting HIV over several years of treatment with cryoprecipitates. The risk of contraction was one per thousand if treated for one year. The risk of contracting HCV was 76 per thousand after one year of treatment, and one in 13.2 if treated for 10 years with cryo. These risk levels are unacceptably high by the standards of developed countries, he conceded. However, a large proportion of people with hemophilia worldwide still have no choice but to use cryoprecipitate.

High purity levels are convenient and desirable, he said, but are not essential. However, since it's not possible to characterize batches, efficient and well-characterized process validation is essential. This will ensure that good manufacturing processes are employed and allow for a degree of consistency, control, and predictability.

Cryoprecipitate's resistance to viral inactivation techniques poses a more difficult problem, he said. However, there are some methods that can be used to treat cryo, which include dry heat treatment or methylene blue/ultra violet treatment. Since all the viral inactivation techniques reduce yields, Dr. Farrugia stressed the importance of improving



yields in conjunction with improving viral inactivation.

In order to address these concerns, the WFH Blood Products Safety, Supply and Availability Committee has established a Safe Cryo Project, which will review cryo use and production from the perspective of quality and safety. It will include review of donor selection, plasma quarantine, review and assessment of technologies to increase yield and safety. To have enhanced safety through viral inactivation, it will be necessary to improve yield, he said. "It's not much good having a safe product, if there's not enough of it left in the end."

Some possible approaches could include optimizing blood collection and preservation, fast freezing, and optimal thawing. The committee will also review possible viral inactivation through methylene blue, heat, and irradiation, he said. It's critical to weigh whether or not decreased yields balance the safety considerations. He cited studies, which indicated that the use of methylene-blue photo-inactivated plasma had increased the demand for plasma and cryoprecipitate because of its low hemostatic quality.

Whenever possible, he continued, plasma should be quarantined until the donor is recalled and retested. Whenever possible, donors should be selected from low-risk populations. Pools of dedicated plasma donors, carefully selected and repeatedly tested, can be a very safe source of raw materials.

Dr. Farrugia concluded that small pool freeze-dried cryoprecipitate is a viable option for treatment in countries that lack the access to or financial means for fractionation. Careful attention to production and collection techniques can allow sufficient product generation to deal with most countries' requirements. Since product safety can't be ensured through viral inactivation, he reiterated the importance of donor selection and screening measures.

Plenary Discussion

Mr. Mindell polled participants on several issues.

Is the goal of zero tolerance inherently at odds with the pursuit of increased supply and affordability?

(Developing Countries Only)

Yes: 67%

No Opinion: 7%

No: 26%

(All Participants)

Yes: 72%

No Opinion: 7%

No: 21%

Are you less concerned about transmissibility of vCJD than you were two years ago?

Yes: 81%

No Opinion: 2%

No: 17%

Is it worthwhile to pursue safer cryoprecipitate?

Yes: 72%

No opinion: 2%

No: 26%

If safe cryoprecipitate could be developed, would it be more affordable than current factor concentrates?

Yes: 48%

No opinion: 19%

No: 33%



Open Forum Discussion

Chair: Albert Farrugia, Blood Safety Advisor, World Federation of Hemophilia

Dr. Farrugia invited several participants to the podium. He posed the first question to Theo Evers, asking about the shortcomings and limitations of relying on a pool of voluntary donors for source plasma. Mr. Evers noted that about 10 years ago, there was a substantial reduction in the number of plasmapheresis activities within the EPFA member organizations. However, in more recent years, these have been increased. In Belgium, for example, a high percentage of its source plasma was collected by plasmapheresis.

The Australian Red Cross Blood Services Organization, an associate member organization of EPFA, he said, also collects a significant amount through plasmapheresis. These countries have achieved self-sufficiency. He cautioned that no one had raised a definition of self-sufficiency and suggested that the term may have different meanings for different people. Several member organizations of EPFA engage in activities with people in other parts of the world, ranging from contract fractionation to technology transfer. In addition, many are members of international bodies and are involved in helping other countries to upgrade their plasmapheresis capacities.

Dr. Farrugia addressed Luiz Amorim from Brazil. It appears, he said, that Brazil's current capacity for self-sufficiency and adequate FVIII supply is one IU per person. Does this imply that Brazil will eventually be aiming for a higher target, since in the developed world the current standard is 3 to 5 IU per person?

Dr. Amorim replied that self-sufficiency is a constantly evolving concept. Brazil does not set its targets in terms of IU per capita, but in terms of IU per person with hemophilia. The target for self-sufficiency, therefore, is 30 thousand IU per person with hemophilia. If you compare this figure with the incidence of hemophilia in the developed world, he said, you'll note that the goal is higher than it seems, since there is a lower incidence of hemophilia in Brazil than in other parts of the developed world. He also pointed out that Brazil is currently working with a 10- to 20-year plan, so it's

likely that standards may change as the situation evolves.

Charles Waller noted that many of today's concepts of self-sufficiency were developed in a different age, when the treatment of hemophilia defined the amount of plasma that was needed. Today, by contrast, that level is not determined by FVIII but by the level of immunoglobulin and alternative products. As a result, the self-sufficiency discussion has different terms in the developing world where it is still very much defined in terms of FVIII than in the developed world.

Dr. Farrugia noted that Brazil is aiming for a plant with a capacity of 500 tonnes. He noted that patients with hemophilia and sickle cell anemia were identified as target groups. He asked Dr. Amorim what considerations were made for patients needing immunoglobulin. Dr. Amorim replied that immunoglobulin is treated differently than FVIII. Whereas FVIII and other factors are obtained by the central government and distributed to hospitals and treatment centres, immunoglobulin is bought individually by each hospital. Brazil uses very little immunoglobulin, he said. They are not self-sufficient in terms of immunoglobulin and are reluctant to supply more because of the likelihood that it would increase demand and lead to more consumption.

Dr. Farrugia directed a question to Dr. Chudgar from India. He noted that Dr. Chudgar said India's centre is now collecting 50,000 units of blood per year, and the country will ultimately need 25 to 30 of these collection centres. Dr. Farrugia noted that would enable collection of 1.5 million units of blood annually, which would yield 15 red cell concentrates per 10,000 people. He further noted that the WHO has set a minimum standard is 50 red cell units per 10,000 people.

Dr. Chudgar replied that 50,000 units were collected during the first year of the centre's operations. It was built with a 100,000-unit capacity and can be expanded to triple that size. Currently, the centre is using voluntary donors and is endeavouring to build up a pool of repeat voluntary donors. Over time, he said, the collected donations will increase and the facility will be expanded.

Dr. Farrugia referred to Dr. Burnouf's presentation, saying he was struck by the difference between the best- and worst-case scenario costs for production of FVIII. He asked how those costs compared to the cost of making blood bank cryoprecipitate. He



noted that Dr. Partraporn Isarangkura from Thailand has shaped their whole program for supplying virally inactivated freeze-dried cryoprecipitate in that country. He asked her to comment on the relative costs of that product versus the projected costs of FVIII.

Dr. Isarangkura replied that there is general agreement that the best product would be factor concentrate. In Thailand, however, both parents would have to work for an entire month to afford even one vial of factor concentrates for treating their child. There is no shortage of blood donations in Thailand, she continued. So, there is plenty of plasma and the donated quality is quite high since it comes from a pool of non-remunerated voluntary repeat donors. The donations are screened for HIV, HCV, syphilis, and other agents. At the end of the process, she said, the cost for producing a single vial of heat-treated cryoprecipitate is \$.08 per IU. The Red Cross and government further subsidize the cost, so that patients pay only \$.05 per IU.

Dr. Farrugia asked Mr. Bult to comment on the difference in cost between cryoprecipitate at \$.08 per IU and concentrates at \$.20 or more. Mr. Bult said he did not think they are comparable when the whole manufacturing process, the inactivation procedures, and validation work are taken into consideration. He also cautioned against comparing country-specific prices because the economic situation in each country is unique.

Mr. O'Mahony said he was uncomfortable with the discussions, because people from developed countries have the luxury of conducting this debate in a philosophical manner. Upon examining the reality in many of the developing and emerging countries, he noted, cryo is provided free of charge by the government, but concentrate would need to be paid for by the individual patient. Often, he added, cryoprecipitate has no cost associated with it, since it's seen as a byproduct of whole blood collection, so the cost of the source material does not reflect reality. He also noted that there were significant differences in the costs of both cryoprecipitate and concentrates from country to country.

Dr. Farrugia asked Dr. Evatt to comment on the degree to which projected risks have been reflected in clinical practice in populations that have been tested. Dr. Evatt replied that the risk is based on a simple premise: the risk of getting a single unit is based on the number of possible donors who donate during the window period. That risk involves many

different parameters that are part of calculating the model, including the prevalence of first-time donors who have a higher risk of serotransmission. The second issue is the incidence of infection in the local population. The third factor is how the cryo is managed after it's collected. If it's just made into cryo and used, there is a much higher risk than if the product is quarantined until repeat tests can be conducted. Venezuela is one of the few countries that has measured the number of seroconversions over the years and released the data. In its case, the data matched the model predictions very closely.

In response to a question about seroconversion with the single- or triple-unit heat-treated cryoprecipitate in Thailand, Dr. Isarangkura replied that there had been no seroconversions to date. Currently, she said, NAT testing is conducted. Among the first 100,000 tests, they found one positive case, but in the second 100,000 none were found. If it were possible to buy factor concentrate for \$.10 per IU, they would, she said. At any higher cost, however, it makes more sense to pay \$.08 per IU for cryo. She asked representatives of large pharmaceutical companies when it was likely that factor concentrate prices would reach \$.10 per IU. An industry representative replied that this is a specific question that would be best addressed to specific companies, noting this was not the proper forum to address these issues.

Dr. Farrugia asked Dr. Françoise Rossi to outline the particular difficulties in regulating plasma in a single-supplier situation. Dr. Rossi replied that the French fractionator is not the only supplier of plasma products in France. In France, there are over 60 plasma-derived products from several companies. The French fractionator is regulated by the French Health Agency, using the same level of regulatory requirements as the other producers. France observed that the level of regulation of health products was quite low, so they realized the importance of strict regulation. They also developed the concept of the need for independence between the regulator and producer, she said. The French fractionator is considered one of the marketing authorization holders. There is a higher level of scrutiny on the national fractionator than on the private ones because of the responsibility that is shared between the government and fractionator.

Mr. Bult noted that there is a special situation in France as a result of its HIV tragedy. He concurred that France is meeting the requirements set out in various treaties in Europe. He stressed the importance of arriving at one set of standards that can be equally applied and are based on the



regulations that have come forward from the European Medicines Evaluation Agency (EMA). He disagreed that the marketing authorization period is the same for the French fractionator and other licensees, maintaining that for the French producer the period is five years, while it's two years for others. That, he contended, constitutes preferential treatment for domestic manufacturers that are using French plasma.

The difference in the length of renewable marketing authorizations, Dr. Rossi said, was derived from an ethical principle, which has nothing to do with safety. Mr. Waller noted that there are many fewer PPTA products licensed in France than in other European countries of comparable size. He conceded the rule was applied fairly, but called it an unusual place to apply an ethical principle.

Dr. Farrugia observed that CSL from Australia is the second- or third-largest fractionator in the world now. It has evolved from being a uniquely Australian manufacturer three years ago to an organization with bases in Switzerland and one of the largest plasma collection networks in the U.S. He asked how industry representatives felt about the number of players decreasing while the companies still involved get larger and larger. Mr. Waller said that companies tend to consolidate when they can make more profit together than they can individually. The low profitability in the industry means more consolidation, which results in fewer product choices for patients. More providers mean a more vibrant industry that can commit resources to meet new challenges like West Nile. It's important, he said, to ensure that there are enough resources to be able to meet emerging challenges.

Dr. Farrugia asked Jay Epstein of the U.S. Food and Drug Administration if a restricted number of suppliers would result in restrictions of regulators' leverage. Dr. Epstein replied that it is more difficult to regulate sole-source manufacturers. When it is necessary to take action against sole-source producers, which aren't unique to plasma-derived products, there is a higher risk to the supply if ultimate action like ceasing distribution or manufacturing is taken. The ultimate impact on the consumer is adverse because the industry is less robust and because there will tend to be less innovation and, therefore, less product choice.

The most important consideration is whether post-consolidation industry is healthier or not. Healthier

organizations mean more stable sources of supply and better use of resources for innovation.

Ultimately, single-source manufacturers make regulation more complicated, but not impossible, since it requires the use of alternative regulatory means like court action. Mr. Waller reiterated that the production of biologicals is different from other plasma products. The production is expensive, he said, and also extremely sensitive. With plasma derivatives, the product and technological processes are constantly improving and evolving. It is unwise, he said, to be left with single sources or even restricted sources of supply.

Ashok Verma from India said all venues must be explored if choices are to be created for affordable treatment in developing countries. If we accept the hypothesis that the plasma market today is not cryoprecipitate-driven, but is driven by immunoglobulin, then most FVIII is not being utilized, he said. Is it possible to build a state-of-the-art facility in India, similar to the one in Bangkok, and transport harvested cryo paste there where it could be virally inactivated, he asked. The advantage would be the low cost of transporting the cryo paste, and the reduced expense in inactivating small volumes of paste as opposed to tonnes of plasma. He acknowledged there would likely be problems with government regulations, but suggested that the intervention of WFH and other respected international organizations might convince the government of India to consider the import and export of cryoprecipitate. A feasibility study conducted a few years ago found that the only serious impediment was the likely number of failed batches that is non-standard product, Mr. Verma said.

Dr. Farrugia noted that this activity itself would need to be regulated and licensed. The activity already occurs in Australia, where cryo is imported and the country exports products. Dr. Epstein noted that the U.S. also licenses manufacturers to sell cryo paste for further manufacture. Mr. Verma explained that he was making specific reference to Canadian cryoprecipitate. Mr. Bult said he didn't think that FVIII cryo treatment was likely to "go away." However, he said, the best use of resources is to try to find better ways to manufacture concentrates at better prices to improve the level of care for all patients.

Dr. Farrugia noted that Mr. Skinner had pointed out that the level of assurance regarding safety issues



would always depend on whether agents are well known or emerging. He asked for comments about the use of “model viruses.”

From time to time, a participant noted, the possibility of simplifying the tests for viruses is raised, particularly for developing inactivation or partitioning methods. She cautioned that the differences between viruses are substantial and really can't be compared to bacteriology, where it is possible to use markers. If different families of viruses are examined, she said, significant differences among members of the same families can be noted. So with new emerging viruses, it's necessary to determine if their properties are really new or if some “model viruses” exist that can be used. In the case of West Nile virus, it is possible to use bovine virus diarrhea virus (BVDV) as a model for viral behaviour. However, from other perspectives, the differences in the viruses can be significant, so she advised against using marker viruses for viral inactivation.

Dr. Epstein added that the U.S. FDA has not yet established a policy regarding marker viruses, as it is still an evolving issue. There is a general expectation that plasma concentrates are currently West Nile virus-safe, but they are still awaiting data to establish the assurance of safety. The first principle is that the actual agent should be studied whenever that is feasible, he explained. For product approvals, there must be a 10 log clearance overall, where at least one step is viral inactivation, rather than just partition. In addition, the process overall should provide a safety margin between 3 and 5 logs, compared to the worst case for the viral burden in the fractionation pool. Currently, the BVDV model for West Nile is adequate for heat treatment procedures and a set of solvent detergent treatment procedures. In the case of less well-studied procedures, however, the FDA is not prepared to render a judgment due to the lack of robust data. The FDA has also not yet taken a position on whether there needs to be donor screening for West Nile virus, he said.

A participant asked for an explanation of the plasma master file. Glenda Sylvester of the EMEA explained the concept came into existence in the early 1990s. It involves a common set of information on the collection and testing of plasma that will apply to a number of products. The information ranges from epidemiology to collection techniques to shipping to testing. Both industry and regulators welcomed its development, she said.



Paid/Unpaid Donors: Safety and Supply Issues

Chair: David Page, Canadian Hemophilia Society

Paid/Unpaid Donors and Safety

Theo Buunen, European Plasma Fractionation Association

Dr. Cees van der Poel, who was scheduled for this presentation, was unexpectedly detained from the forum, so Dr. Theo Buunen provided an overview.

The issue of paid versus unpaid donors has been at the forefront of discussion in the drafting and amendment of the EU directive on the blood safety, said Dr. Buunen. Past lessons indicated a higher risk of infectious diseases among paid blood donors, leading to the conclusion in 2000 by the EU scientific committee on medical products and medical devices that voluntary unpaid donations seemed to offer greater safety. However, the commissioner for public health and consumer interest, who asserted that recent studies did not substantiate this conclusion, challenged this the following year in the European Parliament. The debate was thus re-opened.

A number of studies were taken into account, including one by Eastlund in *Transfusion*, the first attempt to systematically review the issue. Eastlund's findings were that non-remunerated donations seemed to have the residual risk. On the other hand, the *New England Journal of Medicine* demonstrated in 1999 that the absolute risk of infection per unit transfused has dropped considerably because of new safety measures and prophylaxis. Similar conclusions were drawn in a study of commercial and volunteer blood donations in California, which showed decreased rates of HIV in all donations from 1990 to 1996, although there is a consistent pattern of higher viral markers among paid donations. A Government Accounting Office report on relative risk ratio between paid plasma donations and volunteer donations also suggests that, although risk has been reduced with new safety measures, there appears to remain a constant and higher risk with paid donations.

Sanquin endeavoured to study and update the published data comparing the risk of infectious disease markers among paid and unpaid donors of plasma or blood. It also carried out a trend analysis to determine whether relative risk was increasing or decreasing in time. A review of 28 diverse reports spanning 1968 to 2001 showed an apparent systematic relative risk in both paid and unpaid donations over the value of 1. Sanquin's trend analysis of relative risk ratio over time showed no tendency to decrease in risk over time and concluded that volunteer donations still have a safer risk profile.

In a 2002 study, George Schreiber confirmed the conclusions of the GAO report involving different viral markers in paid and unpaid donations. The introduction of initiatives like qualified donors and inventory holds will reduce the risk of an infectious unit being included in a plasma pool, but even so, a higher risk in paid donors remains, Dr. Buunen noted.

How do these differential risks of an infectious unit reaching the pool translate into additional safety for finished products—the ultimate goal? For labile products, the situation is clear: the risk of an infectious unit escaping detection is the same as the risk of a patient receiving such a unit, Dr. Buunen said. For plasma products, the safety of finished products is only partly determined by the trend of the infectious unit entering the pool; it is also determined by parameters such as the size of plasma pool and, more importantly, the efficacy of inactivation procedures. "The study indicates that the ultimate safety level for finished plasma products is still a matter of debate and needs further analysis, principally because inactivation data are very different for different virus types and production procedures vary."

However, Dr. Buunen concluded by reminding the audience that beyond the scientific data, the safety and supply of all plasma products, whether from paid or unpaid donations, fulfill the safety requirements imposed by the regulatory authorities.

Paid/Unpaid Donors and Safety

George Schreiber, Westat

Blood safety screening has improved dramatically around the world over the years, particularly with the development of appropriate screening tools,



including NAT testing in the last three years, said Dr. Schreiber of Westat.

Beyond paid or unpaid parameters, prevalence rates vary among different demographic groups, which makes donor screening politically challenging. This can be seen most dramatically in the U.S., where the Asian population has about 50 times greater prevalence of Hepatitis B antigen (HbsAg) than the general population. On the other hand, incidence rates are much smaller than prevalence rates.

"These differences are very significant if you're trying to do head-to-head comparisons of different groups," Dr. Schreiber said. "You just can't look at the numbers in isolation." For instance, while HIV prevalence in donations dropped steadily from 1991 to 2002, largely because of improved screening processes, incidence rates among the population did not decrease significantly. For HIV, HCV, and HBV, there is no consistent pattern between prevalence and incidence, Dr. Schreiber said.

In the U.K., 67% of people surveyed indicated that, should they need blood, they would be content if the donor were paid. Being paid or unpaid generally did not make much difference for donors, though lapsed donors were less inclined to give while potential donors were slightly more inclined to give blood if remuneration were involved.

Rather than remuneration, the real issues in the treatment of hemophilia involve whether the plasma pool is equal to whole blood, and source plasma to recovered plasma, Dr. Schreiber said. While testing helps shrink risk, viral inactivation is the key to safer products.

In the U.S., where plasma donations are remunerated, careful safety measures are in place. Donor selection for concentrated blood products takes place in two stages, with a 60-day inventory hold on source plasma between the initial donation and qualification for viral testing. Noting that source plasma donors give about 17 times a year, Dr. Schreiber suggested that removing remuneration would result in product shortages that could not be made up for through unpaid donors, particularly given the spot shortages in whole blood that the U.S. already experiences occasionally.

There are dramatic differences in viral marker rates among first-time and repeat donors of whole blood and plasma, he noted. He suggested that excluding first-time donors could be considered a safety measure. Nonetheless, residual risks of viral transmission remain. Asymptomatic donors who

are negative on the screening tests constitute a major risk for transmission of undetected HCV, HIV, or HBV to plasma products. Residual risk can be considered the estimated probability of a potentially infectious plasma unit entering the manufacturing pool. The 60-day inventory hold and NAT testing are critical to reducing risk.

Another important consideration is that source plasma brings about 850 ml of product, whereas recovered product brings only about 225 ml. It takes three recovered plasma donors to equal one source plasma donor, so the safety and remuneration issue needs to multiply the risk of recovered plasma from unpaid donations by three, because the end user of the product will in fact be exposed to three donors, Dr. Schreiber said.

Risks related to pool size must be taken into account, he said, while reiterating that viral inactivation and removal processes are critical to the elimination of residual risk in finished plasma products. For HIV, HCV, and HBV, the risk of having a potentially contaminated manufacturing pool is of the same order of magnitude for source and recovered plasma, and for remunerated and non-remunerated donations. There has been no case of transmission of viral infection by source plasma derivatives in the U.S. since 1994, attesting to the safety of plasma products.

Transfusion transmission continues to occur though, when viruses slip past NAT testing, such as HBV transmissions in Japan and the U.K., and HCV transmissions. In the U.S., the latest challenge has been the West Nile virus, where 600 cases were picked up among donors, including two cases of transmission to transfusion recipients. When subject to proper screening, there is no evidence of any difference in safety between remunerated and non-remunerated products, he concluded.

Paid/Unpaid Donors and Supply

Charles Waller, Plasma Protein Therapeutics Association

Can plasma be collected without compensating donors? Unequivocally not, said Mr. Waller of PPTA Europe. The amount of plasma needed depends on many factors:

- The epidemiology of the condition being treated and specific plasma requirements



- Domestic ability and willingness to pay for expensive plasma products
- How much product can be extracted from plasma; industry yields vary, not increasing significantly and sometimes decreasing because of new measures such as donor exclusion and inactivation
- Use of recombinant clotting factors
- Level of treatment, which in the EU ranges from 2,000 IU per patient per year, to more than 300,000 IU per patient annually

A lot of the policies on self-sufficiency around the world were developed when FVIII for the treatment of hemophilia was the driving factor for plasma needs, Mr. Waller said. However, this is no longer the case today, as immunoglobulin now determines plasma needs.

The data shows that a substantial number of people around the world (75%) continue to receive sub-optimal treatment and some 300,000 PWH receive no treatment at all. Doubling the amount of plasma collected today would simply be a start to meeting the immense needs for plasma derivatives, Mr. Waller stated.

About 23 million litres of plasma are collected for fractionation yearly. About 14 million litres of the plasma collected for fractionation comes from donors who receive some form of compensation for their time (from days off work in Greece, Italy, France, and Portugal to Internet access and Disneyland tickets in Japan). Many new donors will be needed in order to double the current quantity of plasma for fractionation to meet demands, which translate into one million new plasma donors and more than 37 million new blood donors, Mr. Waller said.

Given the conclusions regarding the safety of compensated plasma donors and the importance of viral inactivation and regulation, the hemophilia community needs to focus on the pressing issue of supply, rather than remuneration, he concluded.

Paid/Unpaid Donors and Supply

Jukka Rautonen, Red Cross Finland

The safety of blood derivative products depends on a chain of activities that includes donor selection, aseptic collection, screening tests, the production process, adequate storage, and usage patterns. The

question of remuneration is only one part of the donor selection process, Dr. Rautonen suggested, while noting that if all factors are constant, unpaid donors present slightly better safety. However, he said that it is fully possible to compensate for this gap by using advanced donor management programs and inventory hold. He noted that even if it were accepted that using unpaid donors would be beneficial, there is a need to determine whether it is possible.

Finland is one of few countries in the world with an adequate domestic supply of plasma—around 70,000 kg for 5.3 million people—collected from unpaid donors. Finland has its own fractionation plant, producing FVIII, FIX, immunoglobulin, and albumin. It has an exceptional safety record for plasma-derived FVIII products. A sound production process is key, Dr. Rautonen said.

Today, although young people diagnosed with hemophilia receive recombinant factor, older PWH tend not to want to switch. Finland collects enough domestic plasma for producing FVIII to meet market needs, however, it has twice had to import products because of production problems. Finland also meets 100% of market needs with domestically produced FIX and albumin; it meets 70% of market needs for IVIG. However, Dr. Rautonen stated that Finland is not self-sufficient in plasma products, since other blood products come from commercial players. He added that Finland is not technologically self-sufficient. Other countries can be considered self-sufficient in plasma collection, but lack fractionation capacity. Dr. Rautonen noted that the frequency of blood donations per capita is consistently higher in developed countries with non-remunerated donations. There is a correlation between unpaid donations and the frequency of donations that indicates that it might be possible to abolish paid donations.

A survey of Finnish blood donors revealed that 99% felt donations must be voluntary. Many of these donors could be lost if a remuneration system were introduced, although new donors would likely be gained. Dr. Rautonen noted that when Austria abolished remuneration for platelet collection three years ago, the donor population changed radically, but new donors replaced traditional donors. "There's no question that it can be done," he said. "In theory, it is possible to reach 100% unpaid donations," he continued. "But can it really be translated into practice?"



The major challenges to unpaid collection involve the commercialization of the plasma industry, changes in social climate, and decreased dependence on plasma-derived clotting factors. The wave of consolidation in industry in recent years has made life for small players very difficult, since the significantly different economies of scale bring cost savings, which in turn make possible remuneration incentives for donations. It is understandable that commercial fractionators would want to secure their donor bases, Dr. Rautonen noted. He added that many donors who repeatedly give plasma with altruistic motives come to wonder if they shouldn't be compensated by commercial producers; in many cases, they donate their time and plasma on a weekly basis.

Attitudes towards giving blood are changing around the world, along with changing demands and innovations in products. Reaching a level of 100% unpaid donations might be feasible in the quite distant future, but is clearly not feasible now, Dr. Rautonen said. "While a worthy ethical goal, we should not be willing to sacrifice any patients for that principle." Rather than debate remuneration, hemophilia stakeholders should work together to decide where the limited resources are needed, he concluded.

Plenary Discussion

A very convincing case was made for equivalency of safety in derivative products from paid and unpaid donations because of the controls in place, a participant said. However, he noted that these controls are agent-specific. The 60-day hold period, for instance, is only valuable with detectable markers. He asked Dr. Schreiber to discuss challenges related to emerging agents that might survive the fractionation process, such as a highly lethal non-enveloped virus. Dr. Schreiber replied that the inventory hold is nonetheless a safeguard for picking up viruses, and is better than having no hold period. Even though it is hard to anticipate new viruses, the hold provides the opportunity to respond rapidly to new agents.

Responding to a question about the meaning of comparing prevalence and incidence rates, Dr. Schreiber explained that prevalence is not a good indication of risk, but rather a clinical indication of population risk.

A participant commended the session and said it is important to share scientific data and pitfalls facing the plasma industry and regulators at this time. He expressed major concern with the wide range of treatments from country to country, which in some cases involve amounts that are far beyond the levels required.

Referring to Mr. Waller's indication that the driving factor for plasma collection is now IVIG, a participant suggested that driving factors are evolving and fractionators aim to produce several products and develop a niche. He expressed concern that plasma collection and fractionation and FVIII production will decrease, including for the developing world.

An audience member said that the high cost of plasma, increasing with each new quality and safety measure, needs to be addressed. Can plasma manufacturing costs, which account for close to 50% of the finished product, be controlled? How does the drive for specialty products affect plasma yield? "If we are not changing the way we do business, we will lose the impact of serving patients as we did over the past few years, and continue to struggle with economic issues in the forthcoming years," he said.

What can be done to attract more new, young, non-remunerated, voluntary donors, a participant asked. What will be the impact on those in the hemophilia community who depend on plasma-derived products if this is not achieved? The impact will vary from country to country and how each one approaches source plasma and safety issues, Dr. Rautonen said.

A participant said that equating unpaid donations with ethics is an excellent philosophical position; however, equating ethics with quality presents some difficulties. Self-sufficiency in non-remunerated plasma in the 1980s did not spare PWH in Belgium from HIV and HCV infections.

An audience member said that the developing world relies on plasma-derived products simply because it is cheaper. The WFH has a critical role in helping countries and regions determine the best way to improve care for the 75% of PWH who receive little or no treatment, she said.



Self-Sufficiency in Plasma and Fractionation in Established Markets

Chair: Paul Giangrande, VP Medical, World Federation of Hemophilia

Self-Sufficiency in Established Markets

Theo Buunen, President, European Plasma Fractionators' Association

Even in established markets, said Dr. Buunen, the supply of plasma products can be a source of serious concern, which places plasma products in a very special niche in western health care. Plasma products have several characteristics that may be responsible for their special position.

Plasma products are crucial, even indispensable, for modern health care and will continue to be necessary in the future even with the development and evolution of recombinants, he said. There are no alternative treatments. Their manufacture requires a complex technology with the added complication that the products are derived from donated material and produced in a heavily regulated environment.

Moreover, the donor material is scarce since it has special properties. There are both biological and ethical issues surrounding the collection of source material, which further complicates the issue. The organization of supply presents a number of unique challenges that necessitate special safeguards to ensure adequate and robust supply of safe products.

Because plasma products are indispensable, Dr. Buunen continued, product shortages can have serious consequences. On a number of occasions in the past, patients and physicians have experienced limited availability of immunoglobulins and clotting factors, even in established markets. The causes and duration of these shortages can vary greatly.

In western nations the limitations of supply are often due to limited national or personal healthcare budgets, just as they are in developing nations, he

said. There are also supply problems caused by practical problems in manufacture or supply.

Dr. Buunen noted the importance of distinguishing between the different reasons for limited availability when discussing the possible role of supply self-sufficiency. From a suppliers' perspective, it is preferable to view self-sufficiency as a way by which the supply chain is optimized within existing financial constraints that are of an external nature beyond the manufacturer's control.

Dr. Buunen also elaborated on the concept of adequate supply. To determine what level of supply is sufficient, it's necessary to view it from several different perspectives:

- Patients and physicians think supply is adequate if the medical need for the product is satisfied.
- Governments want to optimize balanced care that satisfies needs determined by evidence-based medicine.
- Insurers use the concept of "appropriate use" on the basis of financial issues.
- Manufacturers see adequate supply as depending on the willingness of the customer to pay a particular price and purchase a particular volume.

Dr. Buunen contended that the definition of an adequate supply from a national point of view should follow the patients' and physicians' view. Manufacturers cannot ignore governments' or insurers' views, he conceded, so there is a need to strike a balance.

The marketplace currently guides organization of the supply chain in established markets, he said, because it is seen as the most efficient way to balance supply and demand in general. The market for source material can be distinguished from the market for product. It is not really an open marketplace since 60% of the source material is donated, while the other 40% of plasmapheresis plasma comes mostly from a limited geographic area (the U.S.A.). Production facilities are also becoming more and more concentrated in a decreasing number of large facilities. It all boils down to a situation where collection, preparation, and production take place in very different regulatory environments. This organization of supply can have consequences for countries that see these developments as possible loss of control over the supply of indispensable products.



The global market has several effects on the availability of product in established markets, Dr. Buunen said. Because “demand rules,” there is the expectation in western Europe that price will drift to the same level as international or global prices. For some countries this can be difficult because they cannot afford those pricing trends. Market forces also tend to mean that “products will follow the highest price,” which can lead to shortages in other areas. The global market for plasma products not only leads to consolidation on a global level, but to specialization. Some countries are already focusing on particular supply areas. This leads to decreasing ability of countries to have control over the whole chain.

This situation is very different with chemical pharmaceuticals, he said. However, for plasma products the availability of source material is a specific problem requiring special control. In a global market, even a local crisis can have a global effect. An emerging disease in a country that is a major collector can lead to worldwide product shortages. The fear that this inspires has led many countries to more closely examine the supply system.

This has led many nations to the conclusion that self-sufficiency can take away some of the adverse aspects of the global marketplace, Dr. Buunen said. Most nations base their self-sufficiency policies on several key elements:

- Blood and plasma are seen as a strategic resource.
- Source material is usually collected by a single organization under government regulation or supervision.
- There tends to be a single manufacturer.
- Import restrictions are put in place for safety reasons, to safeguard supply or to protect the role of the sole manufacturer.
- Export controls are used to protect supplies of the scarce source material for national means.
- There is also a tendency to use governments to influence demand.

Self-sufficiency has several advantages, he observed. The feeling of control over the source material also results in the spread of collection over a number of smaller regions. This control of the source material allows the prevention of the spread of infectious agents from one limited geographical area to other areas. Self-sufficiency also allows countries the opportunity to influence the pricing and cost of plasma products.

There are also, he conceded, several serious disadvantages to this classical approach:

- A single source supplier limits the choice of products.
- The supply is vulnerable in the event of safety incidents or production problems.
- The lack of competition inhibits innovation.

The special character of plasma products makes it inadvisable to leave control over supply of safe products completely to the unbridled effects of the global market, he said. There is a role for “sufficiency” policies, but not for “self-sufficiency” in the single-source classic sense.

In the European context, he suggested, blood will continue to be seen as a national strategic resource. Plasma for fractionation may, in time, come to be seen as a European strategic resource. The harmonization of the quality of blood collection over Europe has been given a very important stimulus through the EU directive that’s being implemented currently. The time has come to work together to look at better ways to organize supply. The collection of sufficient plasma for fractionation in Europe could be addressed pragmatically by establishing national collection strategies that, added together, would result in an adequate and robust supply.

Europe would also benefit from a better harmonization of regulations, rather than minimum standards, Dr. Buunen said. A European sufficiency strategy will also require some discussion about the minimum number of production facilities that should be present within a regulatory environment. It’s important, though, to ensure that the industry, whether it be for-profit or not-for-profit, be compensated adequately to ensure its survival. Such a strategy would allow Europe to avoid the negative effects of the global market, while not steering away from the market as the basic tool for balancing supply and demand.

Our Common Goal: Access to Safe and Reliable Product Supply

Ruedi Wäger, CEO and President, Aventis, Behring, LLC

Dr. Wäger prefaced his remarks by saying he understood that the motivation for self-sufficiency policies



is related to fears that patients have as a result of past events. He conceded that very slow-moving scientific investigation, lagging medical judgment, and a lack of proactive response on the part of the industry led to a disaster in the 1980s. However, he questioned whether self-sufficiency is the appropriate response to that history or an adequate approach for the future.

He cited Dr. Farrugia's earlier comment that the use of domestic products does not guarantee there will be no new pathogens. The discussion as it is sometimes framed (for example, regarding compensated versus non-compensated donations), does not address the real issues. The important discussion must focus on all levels of the value chain from collecting plasma to testing to storing and shipping; in short, all steps in the manufacture and the quality systems.

Dr. Wäger also said there are competing interests among different commercial parties. Manufacturers want to have access to all markets so that patients can have more choice, because patients have the right to choose the best products for their treatments.

A choice must be made, he said, between self-sufficiency and access to care. By and large, Dr. Wäger said he agrees with Dr. Buunen's comments: that in the best interests of all parties, products for blood transfusion (red cells, platelets, etc.) should focus on local collection and manufacturing. He expressed concern, however, that a reliance on self-sufficiency will make it impossible to optimally exploit all the components in human plasma because very few manufacturers are able to use all the fractions efficiently.

The patient community has a right, not just to adequate supply, but also to the best products available. Self-sufficiency threatens to reduce innovation, he said, and regulation/legislation of this nature is not in the best interests of patients.

He conceded that hemophilia patients need trust in products and manufacturers and need to believe there will never be a repeat of the mistakes of the past. However, they also need continuous improvement and innovation of products and improved and evolving safety and quality measures. The most innovative technologies, such as heat treatment, PCR testing, and novel products, have come from large commercial companies. Those innovations could only have come about in an environment of global competition.

Dr. Wäger described the evolution of the EU Directive on Blood as a painful, but healthy, process in which it was discovered that all stakeholders have common interests. Those interests include an adequate supply and safe, high-quality products. The process also provided a chance to highlight important differences between transfusion and plasma products and the safety issues associated with each. However, he contended, it's time to "raise the bar," and address the big differences that exist among EU countries.

The development of the Directive taught all involved parties several important lessons, Dr. Wäger continued. It reinforced the importance of open dialogue between all stakeholders, including patients, manufactures, scientists, and legislators, and underlined the need to continue to work together. Industry will be watching carefully to see how the Blood Directive is implemented, particularly in certain countries, he said.

The EMEA position clearly states there is no evidence of viral safety differences between blood collected from compensated or non-compensated donors, Dr. Wäger pointed out. It also concedes that there is no way to ensure adequate supply from non-compensated donors only. Yet, despite this understanding, some governments and NGOs still fight for sole reliance on non-compensated donor pools and self-sufficiency, he said.

All manufacturers must shift their focus to ensuring that all plasma is collected from healthy donors, rather than focusing on whether they are compensated or not, he said. Compensation is one way of encouraging healthy donors to make repeat donations. Repeat donors are an integral part of the quality and safety process, without which product supply would be severely restricted.

Nearly 20% of his company's 6,000 employees work in quality and safety, Dr. Wäger noted. This is a huge but legitimate expense because the company wants to go beyond regulatory standards to make the safest products possible. There is a point at which excessive attention to safety issues ceases to be in the interest of patients. It would be sensible to reduce practices that have no measurable outcomes on quality or safety, particularly repetitive testing at local levels.

Regulatory harmonization is urgently needed, he said. More common global standards would eliminate patient fears of shortages, while not negatively affecting safety or quality.



Harmonization needs to address five key areas:

- Plasma collection and testing;
- Manufacturing and compliance;
- Pathogen safety and viral inactivation;
- Clinical trials; and
- Product labelling.

Dr. Wäger reiterated that self-sufficiency is an impediment to patient access to the best products. He praised the evolution of the EU directive and expressed hope that dialogue with patients would continue to help regain trust.

He concluded with some comments about Japan's new Blood Law, which, he said raises two major concerns. The first is that the policy will result in reductions in innovation, safety, and quality, while leading to increased cost. The second is with the labelling provisions. Either plasma is of the highest quality and is safe to use, or it is not. Using designations like *kenketsu* and *hikenketsu* are meaningless, and will serve only to confuse and misinform patients.

Self-Sufficiency in Japan

Jugo Hanai, Director, Medical Care and Human Rights Network

Through an interpreter, Mr. Hanai thanked patient networks from across the world whose assistance and support helped Japan attain its new Blood Law. He then presented a brief overview of the history of hemophilia treatment in Japan:

- In the 1950s, treatment was through arm-to-arm transfusion or blood banking with paid donors. Late in that decade, a new law was passed forbidding blood brokerage.
- In the 1960s, the single biggest incident in blood transfusion history occurred in Japan, when the U.S. ambassador contracted Hepatitis B from a transfusion. This led to a Cabinet decision mandating voluntary blood donation.
- In the 1970s, self-sufficiency for blood transfusions through a pool of voluntary donors was achieved, but not for hemophilia patients. The use of cryoprecipitate began, and by the end of

the decade, a sudden increase in plasma importation was experienced.

- In the 1980s, the amount of plasma imported by Japan got larger and larger, until the Japanese were called "the vampires of the world." Japan consumed nearly one-third of the world supply of albumin. Heat-treated products were approved for use after HIV transmission occurred from unheated concentrates. A plasmapheresis program began.

- In the 1990s, the country achieved self-sufficiency for FVIII through voluntary blood donations. The use of rFVIII was approved.

In 1996, an HIV settlement was reached and litigation ended. The Minister of Health and Welfare apologized to those affected. AIDS had a big impact on the hemophilia community in Japan, he noted. Around the time of the HIV settlement, the number of people dying from hemophilia decreased substantially and the government focused more attention on hemophilia treatment. In 2001, there were 4,860 patients being treated for hemophilia; 1,425 had been infected with HIV and 542 had died.

These historic events, Mr. Hanai explained, led to the most recent changes in the Japanese blood affairs laws. A series of three distinct laws was adopted. The first was an act for securing a stable and safe supply of blood from non-remunerated donors, self-sufficiency, and the appropriate use of blood and blood products. The second was an act revising the Medical Pharmaceuticals Act, which created production and labelling standards for biologics. The third created an independent administrative corporation, operating under the Ministry of Health, Education, and Welfare, which would provide oversight for medical pharmaceutical products and medical devices and instruments.

Mr. Hanai explained that the Act for Securing the Stable and Safe Supply of Blood defines self-sufficiency as meaning that, "blood products for domestic consumption are manufactured using source material that is voluntary, non-remunerated, and from within the country."

Safety issues are covered in the Medical Pharmaceuticals Act, he added. The specific issues are implemented through a set of regulations. Among their requirements is the need to keep



medical records for 20 years, and product manufacturing and distribution records for 30 years. They also mandate the reporting of actual or “threatened” infectious disease, and require manufacturers and distributors to report regularly regarding the state of the art regarding infectious diseases. An important breakthrough, he said, is that the committee that oversees much of the regulatory regime has two hemophilia patients on it.

The regulations also make it mandatory for health-care workers to report side effects and safety information, he said.

The regulations around inserts and labelling seem to have caused the most concern from the international community, Mr. Hanai said. They require inserts to include infectious disease risk warnings, the necessity of informed consent, the origin of the biologics, including the name of the creature from which they were obtained, the parts of the body, genetic modifications or engineering (if any), and, if the source material is human-based, the country of collection and whether it was collected from voluntary, unpaid donors. The labels also require the product to be *kenketsu* or *hikenketsu*.

The designation of products as *kenketsu* or *hikenketsu* seems to be very problematic for some people, Mr. Hanai noted. He explained that the committee advising the legislature regarding the new blood laws was looking for a way to take some of the “negative flavour” out of the term, “paid donor,” because it seemed to imply people were donating out of greed only. The reality, he said, is that even paid donors don’t do it just for the money, but also out of a sense of altruism. At the same time, the committee wanted to praise the good will of those who voluntarily donated without payment to let them know that their sacrifice was understood and appreciated. The patients on the advisory committee and the other members saw the use of the term, *kenketsu*, as a way of saying thank you to the voluntary donors.

Mr. Hanai apologized for the fact that the translation of some aspects of the new blood laws had created the incorrect impression that the new law strongly recommends that patients and doctors use domestic products for safety reasons.

Mr. Hanai identified some of the trends for product use in Japan. Currently recombinant and plasma are about equally used. However, the use of recombinant is likely to continue to increase. For

this reason, the new laws apply to recombinant as well as plasma-derived products.

Mr. Hanai concluded by observing that scientists, doctors, and politicians often understand the world differently than patients. From a patient perspective, he said, it doesn’t matter if a product is plasma-derived or recombinant; all that’s important is safety, adequate supply, and quality. It is important to keep pace with new developments while remaining flexible and it’s equally important that patients continue to have opportunities to advocate for better hemophilia patient care.

The Australian Approach to Self-Sufficiency

Albert Farrugia, Blood Safety Advisor, World Federation of Hemophilia

Dr. Farrugia began by presenting a basic overview of the political, geographic, and social situation in Australia. He drew particular attention to the fact that the government is the prime deliverer of most social services, including health care, which is primarily overseen by individual state governments. Australia’s blood supplier is a monopoly provider through the Australian Red Cross Blood Service, funded directly by the governments of the various states and territories.

Up until relatively recently, the only reference to self-sufficiency in Australia was contained in Appendix 19 of the Regulatory Guidelines. That appendix articulates “a policy of not being reliant on donors in other countries is not only in the national interest but an international responsibility.” It goes on to say that, unless there is a demonstrable benefit, the product will not be licensed for distribution by the Regulatory Agency.

Dr. Farrugia noted that in the past seven years, the Australian Regulatory Agency has not rejected a single application from outside suppliers, although, he conceded, there had been few applications. The main barrier is not regulation, but reimbursement policy.

In Australia, the government supplies funding for blood products. If hospitals use domestic products, they’re provided free of charge. If they choose imports they must pay for them. Despite these principles, Australia imports a substantial number of blood products and biologics. It is also necessary to



import treatment products for rare bleeding disorders since they are not domestically produced.

The concept of Australian self-sufficiency originated in the World Health Assembly resolution, he said. The real issue, though, is the fear of overseas pathogens. The desirability of self-sufficiency in general is very ingrained in the Australian psyche because of its geographic isolation. It is very comforting from the point of view of the regulator to know the producer is close by, and that intervention can occur easily. Australia also has a long history of protecting manufacturing, so it has also protected its biotechnology sector. He stressed, though, that this was never at the expense of patient care.

Prior to 1995, Dr. Farrugia said, Australia used 1.7 IU of plasma-derived FVIII per capita. With supplementary recombinant added in, he said, the level of consumption was 1.85 IU per capita. By 2000, combined consumption had increased to 3.14 IU per capita. Rather than replace FVIII with recombinant, a decision was made to use recombinant to top up supplies of FVIII and FIX. Demand is rising, but supply is not keeping pace.

In 1999, Dr. Farrugia continued, the government commissioned the Australian Blood Review. It engaged in broad public consultation and reviewed the concept of self-sufficiency. The Review's report recommended that self-sufficiency should continue to be an important goal. As a result, the State, Territorial, and Federal governments in Australia established a new statutory agency, the National Blood Authority. The agency brings together fragmented jurisdictional and financial arrangements. The National Blood Agreement 2003 also reiterates the commitment to self-sufficiency, but not in a draconian way.

In 1999, the Australian Health Ministers' Advisory Council established a Working Party on rFVIII and rFIX, Dr. Farrugia explained. That group included representatives of government and patients. In 2003, it delivered its report. Among its recommendations were the following:

- That the national supply target 3.31 IU per capita for FVIII;
- That current restrictions on access to rFVIII and rFIX be removed as rapidly as possible, and those products be used whenever therapeutically advantageous;
- That a target of 85% recombinant use be reached as soon as possible; and

- That plasma collection targets be established by reference to the clinically justifiable need for IVIG.

In essence, the last recommendation would require the collection of 310 tonnes of plasma annually, he said.

Other expert committee reports regarding HCV and TSE also recommended increased use of recombinant products for safety reasons.

Dr. Farrugia explained some of the unique Australian standards for the domestic plasma industry, which go over and above the minimum standards established in the regulations. Since 1998, a plasma master file has been required. Since the Australian producer (CSL) is now a massive international company conducting contract fractionation, it is now required to segregate international-origin plasma from domestically obtained sources. Double viral inactivation has been mandated, as has the validation of TSE elimination capacity.

In April 2003, Dr. Farrugia said the Therapeutic Goods Administration executed the largest medical recall in history. This created a huge public outcry against the regulator. As a result, the government gave the regulator a broader range of options enforcing regulatory compliance. Those now include penalties for non-compliance, such as fines and imprisonment.

Self-sufficiency is understandable and enshrined within the Australian system, Dr. Farrugia concluded. In recent years, however, the approach has become more flexible. Rather than restricting the regulator's powers, the commitment to self-sufficiency has enhanced them.

Plenary Discussion

A participant noted that Dr. Wäger had said that global regulatory harmonization could result in 15% to 20% cost reductions. He asked if this would translate to a corresponding reduction in product prices. Dr. Wäger said that plasma fractionation is an extremely complicated process. Cutting out regulatory complexities would certainly benefit the whole industry, he said, but price depends on individual companies and what the situation is at any given time.



Another participant said he recently learned the Japanese Red Cross system does an “analogue” inventory hold for six months for recovered, not source, plasma once the whole blood has been centrifuged and administered to the patient. The patient is monitored while the plasma is held. Only after six months does the plasma get sent for fractionation. He said this might be an advantageous approach since it is sometimes difficult to retest the donors.

Dr. Farrugia noted that most recipients of blood transfusions die within six months, which would make the approach problematic. Dr. Wäger said he thought it was an interesting idea, but noted that inventory hold is a very expensive way to ensure safety, and it might be more efficacious to spend the money on other safety measures.

The participant responded that this approach makes sense in a place like Israel, where NAT testing isn’t done. It also has the secondary advantage of providing additional tracking and monitoring of the patient who can get immediate treatment if necessary. Dr. Farrugia replied that he supported assessing adverse events in transfusion and thought this might have real value for the transfusion community. He questioned its efficacy for safety validation, noting that it’s very difficult to establish causality in infectious disease events.

Mr. Hanai said that another reason for the inventory hold was to ensure that there would be excess supply in storage in case of emergency.

Mr. Bult said the Japanese labelling requirements indicated a lack of communication between patients, government, and other stakeholders. He asked how the relationship could be improved. Mr. Hanai noted that his committee’s intent was to distinguish between those who had voluntarily donated without compensation (kenketsu) and others. The intent of the labelling had nothing to do with safety, but with acknowledging an act of goodwill. If kenketsu was understood to mean safe or safer, that was a misconception. If there’s confusion, it’s the responsibility of the industry, patient, and treatment communities to make the scientific issues clearer.

Dr. Buunen acknowledged that plasma holding could be expensive and relatively complicated. However, it is worthwhile because if a problem develops an entire six-month supply of plasma does not have to be destroyed.



Closing Plenary Discussion

Chair: Brian O'Mahony, President, World Federation of Hemophilia

Mr. O'Mahony polled the audience on a number of questions aimed at gauging changes of perception or opinion since the start of the forum, and perspectives on future issues.

Is having enough fractionation capacity for national needs a desirable goal?

Yes: 51%
No Opinion: 4%
No: 45%

Is having both plasma and enough fractionation capacity for national needs a desirable goal?

Yes: 58%
No Opinion: 1%
No: 40%

Which is safer?

Paid: 10%
Unpaid: 31%
No Difference: 60%

What is the most critical issue facing the hemophilia community?

Safety: 26%
Supply: 26%
Affordability: 48%

Are you planning to attend the 2004 WFH Congress?

Yes: 73%
Undecided: 21%
No: 6%

Where should the next global forum be held?

Montreal: 12%
Europe: 30%
Elsewhere: 58%

When should the next global forum be held?

April 2005: 33%
September 2005: 44%
November 2005: 22%

Mr. O'Mahony noted the slight increase in the number of participants who now saw fractionation capacity to meet national needs as a desirable goal. However, there was no proportional change in viewpoint on having both plasma and enough fractionation capacity for national needs as a desirable goal. He noted a significant increase in the proportion of participants who felt there was no difference between the safety of paid and unpaid donations. Most interestingly, he said, the position among participants had shifted over the course of the forum, and it was now felt that safety and supply were of equal importance and that affordability is becoming the biggest issue. He then invited comments and questions for the session chairs and speakers.

A participant said that as a first-time attendee of the global forum, she had gained a lot from the presentations and was emerging with a different, more informed viewpoint. She suggested that it may not be possible, or useful, to define self-sufficiency on a general level, since it would vary from country to country and depend on cultural, political, and economic circumstances in each place. Affordability is clearly a critical issue, she said, while asserting that it is directly related to the availability or non-availability of plasma. "It's clear to me that if we don't collect more volume, we can't reduce the price of the product." Historically, promoting public awareness and encouraging blood donation has been seen as the role of blood operators (i.e. Red Cross societies). However, they have been hindered by constraints of time and resources, and the WFH could have a role to play by becoming more active in public initiatives. In conclusion, she noted the difference in safety between first-time and repeated donors, and the importance of figuring out the motivations of repeat donors, since repeat donations can contribute substantially to greater supply, quality, and affordability.

Dr. Evatt noted that the principles of self-sufficiency and voluntary donors were established in a different time. The dramatic expansion of technologies since that time has changed the reality of the issue. He added that no evidence has been presented showing that principles of self-sufficiency and voluntary donations have actually increased blood collection



and capacity. In fact, he said, it is clear that in many places these principles have been barriers.

He agreed that despite the inclination to boil it down to one statement, self-sufficiency and safety standards are country-specific. "The real question is should the WHO reconsider and modify its recommendations in light of what we know about their effects around the world and about the changes in today's technologies and ability to produce safe products. Being self-sufficient in a country where there are high blood-borne infection rates, and refusing plasma imports because they are derived from paid donors, doesn't make sense in terms of patient delivery," he stated.

Dr. Farrugia stated that the use of recovered plasma for fractionation is based on the clear understanding of the safety of plasma derivatives and that many of the so-called risks of first-time versus repeat donors are screened and eliminated during manufacturing. Moreover, this is felt to be the only way of maintaining a sufficient level of supply, particularly in a system that depends on whole blood collection. "In much of the developed world, we have reached a plateau in relation to blood donations. Australia is putting in massive efforts just to maintain current levels and a standard supply of blood." He added that, in his view, "the key is to shove the system into plasmapheresis, which is a totally new paradigm based on recognition of the relative safety between plasma and whole blood."

Dr. Epstein agreed with Dr. Evatt that the translation of self-sufficiency principles into practice is really dependent on local conditions. Noting the intersection between the efforts to make whole blood components safe and efforts to obtain safe plasma, he said: "There are settings where these are very tightly linked and if plasma collection becomes the driver, then the blood components become less safe. That interplay needs to be more carefully examined."

With respect to the drive for self-sufficiency and for non-remunerated voluntary donations, Dr. Epstein concurred with Dr. Evatt and other participants that there is a need for rethinking by the WHO. These principles were brought about in a different time and under different circumstances and "are probably doing at least as much harm as good." However, said Dr. Epstein, the elements that led to these measures are still relevant and warrant consideration in the present debate. For example, ethical donation is still a key issue because it affects donor participation and product stability. "The

principle of ethical donation should not be dismissed—it's a mistake to equate that principle to a safely collected product. Product safety is part of a series of steps that act collectively," he said, echoing similar viewpoints expressed at the forum.

He added that protectionism, despite its so-called evils, does serve a legitimate purpose: that of ensuring a stable supply of quality products. The underlying concepts of ethical donation, ensuring safety, and a stable supply of quality product, remain valid. The question is whether the over-arching principles of self-sufficiency and non-remunerated donations are serving those aims in the current context. Sometimes yes, sometimes no, he said. The principle can no longer be a one-size-fits-all global recommendation.

The issue of supply is inter-related with what is considered adequate treatment, since these standards determine the supply required, Dr. Srivastava said. In 1996, for instance, 1 to 2 IU of factor per capita was considered a good volume, but in recent years this has risen to 2 to 5 IU per capita. This does not necessarily translate to better long-term outcomes, he noted. It is important to recognize that the current definition of what's optimal treatment will predict supply requirements.

Supply and affordability are inter-related issues that urgently need to be addressed, said an audience member. He suggested a global pricing strategy that would provide for factor concentrates and blood products for the developing world at humanitarian prices, rather than commercial or at cost prices. "It would go far in addressing a situation that seems totally hopeless," he said. Beyond increasing collection, supply can be augmented by improving the yield of the plasma already being collected, said Mr. Page. He pointed to the Canadian cryoprecipitate that is not being used and should not be wasted as just one way to improve supply.

An audience member said plasma products volumes from both remunerated and non-remunerated donations have been flat for the past decade. Over the past five years, however, the cost of source plasma has risen by more than 50%. He added that there is no end in sight to rising costs even if volume is driven up. He agreed with Dr. Farrugia that the most efficient way to obtain a safe supply and adequate volume is by plasmapheresis, and this has been most cost-effectively achieved in large fractionation centres that have frequent donors.



In closing, Mr. O'Mahony asked a final question of participants:

How did you find the 2003 global forum?

Exceeded expectations: 50%

Met expectations: 44%

Disappointed: 6%

The 2003 global forum helped focus perspective on the issue of self-sufficiency, Mr. O'Mahony said, noting the change in view on the relative safety of remunerated versus non-remunerated donors. He added, "We've also seen a recognition that supply and affordability are as important as safety." The global forum in 2005 will address issues and barriers related to supply and affordability, among other emerging topics, he said. He thanked the WFH blood safety and supply committee for their work on the forum. He particularly thanked David Page, chair of the 2003 Global Forum, and Mark Brooker, WFH public policy officer, for their collaborative work behind the scenes, quipping that they make a fine example of how voluntary and remunerated resources can co-exist well together.

