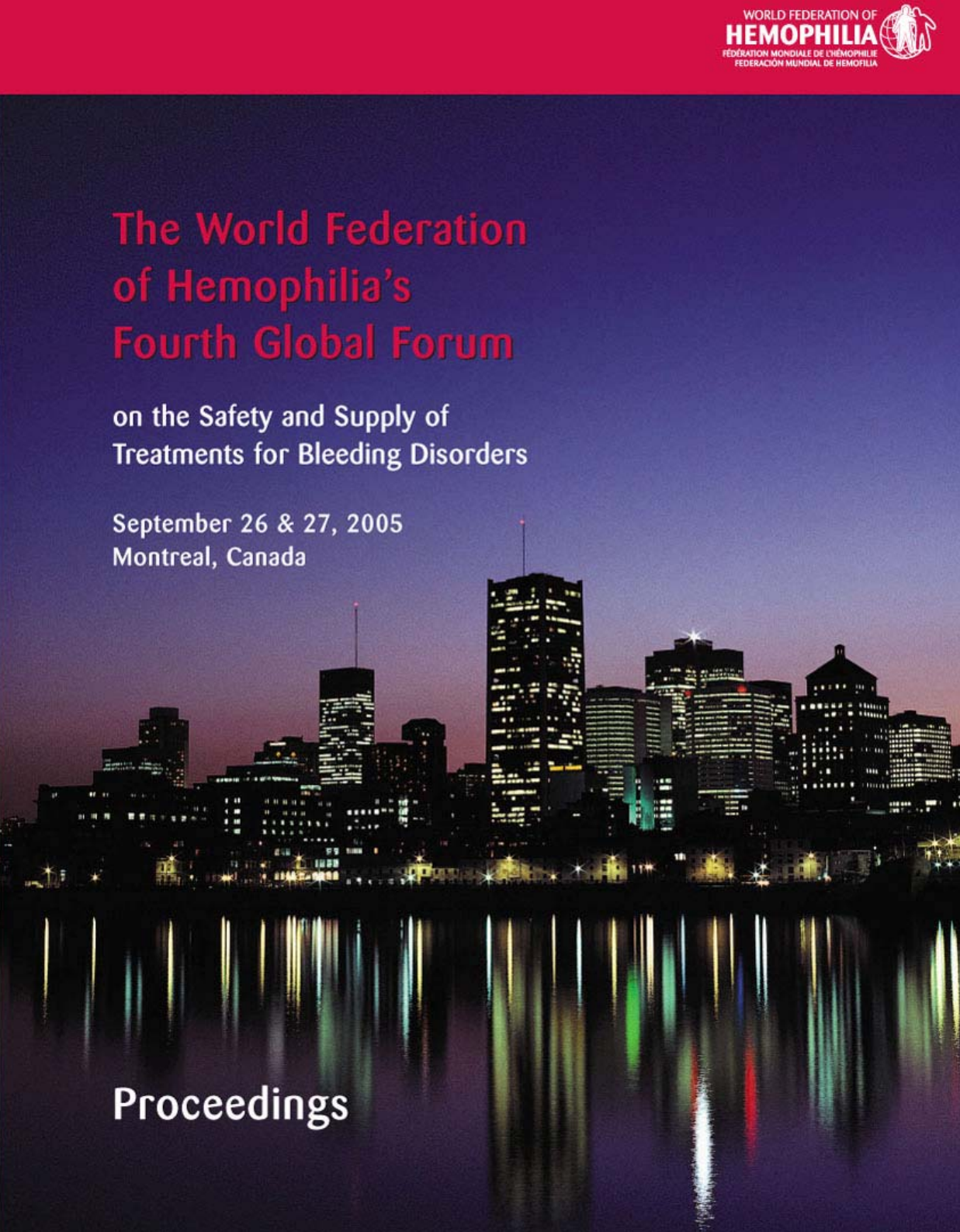


The World Federation of Hemophilia's Fourth Global Forum

on the Safety and Supply of
Treatments for Bleeding Disorders

September 26 & 27, 2005
Montreal, Canada



Proceedings

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Executive Summary

World Federation of Hemophilia's Fourth Global Forum on the Safety and Supply of Treatment Products for Bleeding Disorders, September 26–27, 2005, Montreal, Canada

“Increasing the world-wide supply of safe affordable factor replacement therapy” was the focus for 128 representatives of patient organizations, regulatory agencies, industry, clinicians, and other stakeholders at the World Federation of Hemophilia's Fourth Global Forum. WFH president Mark Skinner declared the Forum a good start to working towards safe affordable treatment for all people with bleeding disorders. He said that the Forum had pulled together a “winning coalition” of stakeholders that will be able to work together to make a difference for people with hemophilia and other bleeding disorders. Mr. Skinner highlighted the WFH's multivariate approach to increasing global access to sufficient supplies of a range of safe, affordable treatment products which involves:

- Management of existing resources
- Utilization of all treatment options
- Developing the patient community both through identifying new patient populations and new indications
- Reducing manufacturing cost
- Innovative pricing structures
- Humanitarian aid

Dose and Outcome in Hemophilia Care (A. Srivastava)

Dr. Srivastava gave an extensive overview of the key questions and available evidence relating to optimal treatment. A study in 2004 showed that the use of clotting factor concentrates has risen to between 6 and 7 international units (IU) per capita from between 2 and 4 IU per capita. This increase comes with enormous cost implications, and raises the question of whether increasing the dose to that level is really necessary. Long-term data on the outcomes of various doses in terms of quality of life are lacking. Currently, 40% of the world uses less than 2% of the global supply of factor concentrates. Dr. Srivastava posed the question, how can hemophilia be managed more cost-effectively? In order to do so, he noted, a shift is needed in the way that the outcomes of various doses are documented and the way in which outcomes are measured—particularly in terms of musculoskeletal function and quality of life.

Trends in the Plasma-Derived and Recombinant Markets (P. Mannucci and A. Farrugia)

A little over a decade after the approval of the first recombinant clotting factor, the plasma proteins market has seen significant adjustments. Evidence suggests that plasma-derived products are much safer than in the past. For example, fractionation has a good capacity to remove prions and there has been no documentation of prion transmission by plasma-derived products. Nonetheless, recent experience shows that pathogens will continue to emerge and re-emerge. Factor concentrates from pharmaceutical manufacturers are subject to manufacturing and quality control processes that are similar for plasma-derived and recombinant products alike. In fact, the plasma industry may be the most regulated of the pharmaceutical sector.

Preliminary data from retrospective studies indicate that previously untreated patients who received large amounts of von Willebrand factor showed a lower incidence of inhibitor risk, Dr. Mannucci said. Other findings suggest that switching patients from one product to another is not a good practice, because use of multiple products may be linked to a higher incidence of inhibitor development than is use of single products. Inhibitor risk is currently the foremost safety issue for regulators, Prof. Farrugia concluded.

Extremely Rare Disorders (D. DiMichele and P. Bolton-Maggs)

The first steps in global collaboration to gather data on extremely rare bleeding disorders, such as deficiencies of FII, FVII, FX, FV, FXIII, and fibrinogen and the dysfibrinogenemias were discussed. Early work has found that the treatment used most often for rare bleeding disorders is fresh-frozen plasma (FFP) and cryoprecipitate, with activated prothrombin concentrates for vitamin K-dependent patients. Various treatment-related complications occurred, including some allergic reactions with the heavy use of plasma-derived products. An issue that the North American Rare Bleeding Disorders Registry brought to light was that FVII is one of the more frequent of rare bleeding disorders. But at that time, Dr. DiMichele noted, neither FVII plasma concentrate nor recombinant factor was available in the United States for that indication.

There are discrepancies in the availability of treatment for rare bleeding disorders. For example, preliminary data from the North American and European registries show that hardly any treatment was administered in the United States, but that, in Europe, a variety of plasma products—and in some cases, recombinant products—were administered. Generally, rare disorders present a less clear correlation between bleeding and factor levels, making management more difficult. Dr. Bolton-Maggs observed that advances are being made in data collection but she urged further international collaboration for these extremely rare coagulopathies.

Unused Proteins (T. Burnouf, G. Sher, and D. Armstrong)

The WFH is encouraging plasma collectors and fractionators to find ways to manufacture and distribute proteins that are currently being unused. For example, in some countries where people with hemophilia are treated with recombinant products, factor VIII is no longer produced from the donated plasma collected by the domestic blood service. Dr. Burnouf explained that the available unused plasma comes mostly from whole-blood donations. Of the roughly 16 million litres of plasma collected annually worldwide, 3 million litres are used for transfusion, leaving 13 million litres for fractionation. Approximately half of this 13 million litres is actually fractionated, mostly in developed countries. Part of what remains is used to make cryoprecipitate and blood bank plasma. Most of the available material does not meet the quality criteria of fractionators or national regulatory authorities for testing, freezing, and storage conditions. Dr. Burnouf warned that significant regulatory work would be required to qualify this plasma as a source for medicinal products. The cost and quantity of the source material, plus the manufacturing costs, must yield a return on sales, which requires economies of scale.

With respect to WFH's commitment to explore the use of recovered plasma for the extraction of FVIII and other proteins, discussions are underway with Canadian Blood Services and Héma-Québec and National BioProducts Institute (NBI) in South Africa to process unused Canadian proteins. Currently, NBI produces intermediate-purity, solvent-detergent-treated FVIII and solvent-detergent-treated FIX prothrombin complex. These products can be stored at room temperature to accommodate their many clients who lack refrigeration.

Better, Safer Cryo (G. Rock)

Cryoprecipitate is still used to treat patients in many countries. It is not safe but it is easier to produce and has some efficacy and can be used in life-saving situations. Because cryo is used to treat people with bleeding disorders, it is worth looking at ways to make it as safe and efficacious as possible. During the first 24 hours after donation, FVIII activity decreases by 50%; however, after that, it becomes relatively stable. Also, FVIII levels in whole blood are not much different at 22°C and at 4°C. “Buffy coat” production requires material to be held for 24 hours before processing, which results in a 50% yield reduction in FVIII. The process for making cryo is simple. Plasma is frozen, thawed, and then centrifuged; the cryo is then removed. However, this process is totally reversible; if cryo is left standing in plasma, even at 4°C, the material will return to solution in its entirety. Dr. Rock asserted that making a better cryo is possible. However, the economics will vary from country to country. During discussion, the risks of using cryo compared to viral inactivated concentrates were reiterated. The safety of cryo is completely reliant on blood banking technique, diligent testing and good manufacturing procedure.

Plasma Standards and Yield (A. Farrugia)

There is considerable international variation in the standards for freezing and storing plasma and there have been calls for regulatory and scientific consensus. Prof. Farrugia described the thinking behind the various standards. Regulatory requirements—particularly those regarding the freezing and storage of plasma—are predicated on the need to preserve the FVIII molecule. A good case can still be made for optimizing FVIII preservation, because—being the most labile therapeutic protein—it is a good marker for overall plasma quality. The marked differences in European plasma standards indicate how difficulties arise when the same material is used for two completely different reasons—notably fractionation and transfusion. The important issue is not the ultimate temperature, but the speed with which that temperature is attained. Empirical evidence suggests that freezing to -30°C within 30 minutes results in higher FVIII yields.

Potency Labelling (T. Barrowcliffe)

There are currently three different ways of labelling. Most of Europe uses nominal value. In the United States, the actual assay value is listed on the vial. Recently, the United Kingdom has required dual labelling, although not on recombinant products. Manufacturers tend to prefer nominal value labelling. Such labelling is easier and provides a clear target for production. Regulators like it because it makes licensing easier. It also makes accounting more straightforward. Patients and clinicians alike find dosage calculations simpler. With actual labelling, the manufacturer is fully paid for each unit in the batch, and patients and doctors can be more certain of the dose. On the other hand, regulators can find it difficult to write licenses. Dr. Barrowcliffe suggested that dual labelling may be best because it allows for more transparency. Regulators then have a good check on the accuracy of the nominal value, and accountants, patients, and treaters know that “what they see is what they get.”

Re-labelling and Re-validation (J. Dodt)

Because clotting factor concentrates are so valuable (life-saving plasma proteins that are expensive to collect and manufacture) the WFH would like to find ways to make sure that clotting factor concentrates which are safe and efficacious are not wasted because of an arbitrary expiry date. Re-labelling would involve assigning a new potency to a product batch at or near its expiry date. The activity or safety profile of a particular product does not undergo a sudden change on its expiry date, but no further knowledge about stability, safety, or efficacy is available beyond the approved expiry date. Re-validation would involve re-labelling under certain validating conditions. This process would require a product to be retested at the end of its shelf life. A new set of shelf-life specifications would be assigned. This process would create more knowledge about the behaviour of

the product. Dr. Dodt stressed that regulators can only approve expiry dates based on evidence. He suggested that currently these decisions could only be made on a case-by-case basis.

Inhibitors in Hemophilia (M. Soucie)

Determining if specific products or categories of products have higher rates of inhibitors is an important issue for the hemophilia community. To test the feasibility of monitoring inhibitor incidence, a group of frequent hemophilia treatment centre (HTC) users was studied. The study indicated that the incidence of inhibitors in previously treated patients is very low. However, despite nearly four years of follow-up, Dr. Soucie said, the study was not able to detect differences in rates between levels of risk factors or to adequately assess differences in rates between products. The Centers for Disease Control (CDC) has designed a pilot study of post-market surveillance for inhibitors. Inhibitor testing and hemophilia gene testing will be done at the CDC. Hopefully, this type of large-population monitoring will be sufficiently powerful to examine a rare event such as inhibitors. To obtain data adequate to identify risk factors and assess product risk, he concluded, international collaboration will be required. During discussion, clinicians expressed interest in collaborating to share international inhibitors data.

Innovation (C. Bryant and B. Chiasson)

The Global Forum heard reports from two of the companies that are developing innovative new technologies. Prometic's Plasma Protein Purification System is a sequence of affinity chromatographic adsorption steps, using synthetic ligands specifically designed for maximum binding with particular target proteins. Seven plasma proteins were initially targeted, but the sequences can be adapted to specific needs, and steps can be omitted if a protein is not needed. The process is a cascade, the plasma (which has not been cryoprecipitated) is loaded onto a column. vWF/FVIII is derived directly by adsorption onto an affinity resin designed to attract it. A similar process occurs for plasminogen, fibrinogen, immunoglobulin G, albumin, and alpha-1 proteinase inhibitor (A1PI). Some of the other considerations that may reduce production costs include a lower plasma requirement for equivalent product yield, a processing temperature of 25°C (rather than -5°C), more-highly automated systems, and the elimination of the ethanol-recovery infrastructure.

Bayer's Next Generation Kogenate is being developed with the aim of extending the period of action of FVIII. Three approaches to enhance activity are being used: activity muteins, binding muteins, and pegylated muteins. To date, the *in vitro* data with activity and binding muteins has been very promising, but *in vivo* studies have been less so. Pegylation results suggest improved recovery in hemophilic mice, but the data are still preliminary. Other current research at Bayer is focused on the development of gene therapy treatment for FIX. FIX is an ideal target: the gene is small and it codes for a stable protein with high potency, but requires low expression levels

vCJD Risk Assessments for Plasma Products (M. Weinstein and D. Page)

Although there is no known case of transmission of variant Creutzfeldt-Jakob disease by plasma-derived products, there have been several widely varying risk assessments made by health authorities. The FDA estimates that a patient receiving 15,000 IU of FXI has an average potential risk of approximately 1 in 7 (with a probability range between 1 in 200 and 1 in 2) of being infected with vCJD. Dr. Weinstein cautioned that the risk assessment is highly uncertain and may even be inaccurate, because how the results from the animal experiments that were used in the risk assessment apply to humans is unknown. Moreover, some individuals infected with the vCJD agent may never become ill with the disease. Finally, no direct studies of vCJD clearance by manufacturing processes have been undertaken.

Mr. Page said that for patients around the world, information and clarity are lacking. The September 2004 communication to patients in United Kingdom specified a 1% or greater risk of being exposed to vCJD through FVIII products. In Canada, it was known that about 50 patients had received FXI products up to 2001. Health Canada had conducted its own risk assessment and concluded that the risk was between 1 in 100,000 and 1 in 1 million. Nonetheless, using the same products from same donors given in same quantities, the Canadian analysis came to different conclusions, and Health Canada recommended that no extra infection control to be taken.

During discussion, it was confirmed the consequences in the United Kingdom were that, after September 2004, some people were refused access to basic dental care and surgery. In addition, public health authorities provided no compensation to hospitals for equipment destroyed as a precautionary measure. A comprehensive global notification requirement for donor plasma may help to ensure that foreigners and nationals are treated equally.

National Tender Systems (B. O'Mahony, J. Bult, S. Rezende, and M. Brooker)

Mr. O'Mahony began the session by outlining the steps and advantages of a tender system. Selection criteria are a crucial part of a good tendering system. These criteria can include price, most economically advantageous tender, and diversity of suppliers. It would be a major concern if clotting factor concentrates were chosen solely on price. Price is one factor, but safety, efficacy, and supply considerations are also key. Selection, based on the most economically advantageous tender where all these criteria, including price, were considered was recommended. The formal involvement of leading clinicians and representatives from national hemophilia organizations is vital.

The Plasma Protein Therapeutics Association (PPTA) strongly supports freedom of choice, patient access to care, open-market principles, and regulatory oversight. The PPTA opposes restriction of choice, preferred-drug lists, sole-vendor contracts, and restriction based on price. "A tender is against all these principles, but sometimes it is the only option available." Another disadvantage of tenders is that no guarantee is given of a consistent supply at the end of the contract. Moreover, Mr. Bult noted, when countries change suppliers, the patient population needs to be put on another therapy. Open markets are the best way to avoid compromising quality and safety, he emphasized – fair game and fair treatment.

The UK Department of Health has been working out a strategy with HTC and local health systems to transfer patients to recombinant products in phases. A working group determined that, to get best possible price and consistency across the country, a national tender should be placed for the products. Information from the National Hemophilia Database helped to determine the precise number of patients with severe hemophilia and the quantity of products used from April 2002 to March 2003. Two companies came up with volume-linked prices one third below the usual. Dr. Bolton-Maggs said the future of the current tendering system is not clear.

A seven-member technical committee, including the president of the Brazilian hemophilia society, academics, and hematologists working in HTCs, oversees tendering in Brazil. The committee is responsible for designing the technical specifications, which are normally approved by the head of coordination of Blood and Blood Products, a division of the Ministry of Health. Brazil's process involves "upside-down bidding," in which the winner is the lowest-priced product that meets the technical specifications. Savings of up to 60% over the previous price have been achieved, Dr. Rezende said.

Around the world, the reported prices for FVIII products varied widely from US\$0.14 to US\$1.80. A similar range was observed for the variety of FIX products (from US\$0.17 to US\$1.75). Median prices ranged from US\$0.60 to US\$1.00 for FVIII products.

Differential Pricing (N. Dhingra)

The WFH is exploring the development of a program of differential pricing for clotting factor concentrates. Dr. Dhingra explained that several approaches are being used by the WHO to reduce the prices of other types of medications: Differential (tiered) pricing, whereby prices are adjusted to reflect purchasing power at their destinations; competition between suppliers; regional and sub-regional procurements; licensing agreements that allow developing countries to produce medicines of the same quality at lower costs; parallel importation, whereby products are bought in countries in which licensing arrangements have set lower prices and then are exported to other countries; and new funding mechanisms from the public and private sector to help pay for treatment. While acknowledging that, "International intellectual property rights are an instrument of public policy," Dr. Dhingra asserted that, "International rights of the person should take precedence over property rights."

One project—for the procurement of antiretroviral drugs—saw WHO assist 19 countries to reach agreements with manufacturers for the provision of lower-priced medicines. In a second case, a vaccine procurement arrangement allowed low-income countries to purchase vaccines more cheaply as the result of a WHO/UNICEF bulk procurement.

WFH Humanitarian Aid Program (C. Black and A. Haffar)

The WFH humanitarian program is the largest and most credible supply channel for donated hemophilia treatment products, last year, donations were channeled to more than 17,000 people in 55 countries. Dr. Haffar said the WFH accepts regulator-approved products from manufacturers, hospitals, and homecare companies. The products must have a minimum of two months' shelf life remaining, although the ideal is six months. Ms. Black said that some of the challenges facing the WFH humanitarian aid program include the constant need for donations, international security concerns, limited shelf life of the products, the unique nature of clotting factor concentrates, and the necessity of finding ways to avoid wasting the potentially life-saving products. The WFH is particularly in need of donated FIX and of products for patients with inhibitors.

Forum Opening

Welcome

Mr. Miklos Fulop, CEO and Executive Director, World Federation of Hemophilia

Mr. Miklos Fulop welcomed more than 130 participants from 30 countries around the world to the Fourth World Federation of Hemophilia (WFH) Global Forum on the safety and supply of treatment products for bleeding disorders. The goal of the forum was to encourage an exchange of knowledge, viewpoints, and perspectives, and to build a common understanding for moving forward, he added.

Opening Address: Overview of the Varying Needs of People with Hemophilia around the World

Mr. Mark Skinner, President, World Federation of Hemophilia

The WFH is making tremendous progress towards determining the prevalence of bleeding disorders, said Mr. Mark Skinner. Diagnoses of patients with hemophilia have increased by 5% globally, and Global Alliance for Progress countries are now diagnosing five new patients daily. Once patients are diagnosed, it is essential to find safe, efficacious, and affordable products with which to treat them. "However, the reality today is that economic capacity drives the availability of concentrates, and 75% of people with hemophilia lack treatment," Mr. Skinner said.

Mr. Skinner reported that, in March 2005, the World Health Organization (WHO) reaffirmed clotting factor concentrates as essential for the treatment of bleeding disorders and as a health care priority for governments around the world. Meeting the worldwide need for safe and affordable factor replacement therapy cannot be accomplished by the WFH alone. It requires a "winning coalition" of patients and their families, health care professionals, governments and health ministries, regulators, and industry, Mr. Skinner said. The WFH builds core expertise in areas such as laboratory diagnosis, data collection and analysis, development of cases for support, and government purchase, tender, or reimbursement. The challenge is whether affordable treatment will follow a diagnosis of hemophilia.

Increasing the worldwide supply requires a multivariate approach that involves managing existing resources, using all treatment options available, reducing manufacturing costs, developing new markets, and structuring prices innovatively so as to make products more affordable for some around the world, and providing humanitarian aid.

The WFH recently published a monograph with guidelines on treatment, which outlines optimal dosing and describes plasma-derived and recombinant products alike as important treatment options for hemophilia and other bleeding disorders. Both product types have a robust safety record, and the supply of either alone is insufficient to meet the global needs, he emphasized. Moreover, "economic capacity dictates what a country can purchase, so it is important that there is a range of products and prices." The supply

shortages of recombinant products several years ago and disruptions from viral infections before that demonstrate that it is important to have a system that is built on flexibility and that relies on both plasma-derived and recombinant products.

In its March 2005 report on essential medicines, WHO cited some safety limitations with regard to cryoprecipitate; however, the reality is that much of the world still uses it, Mr. Skinner said. At the same time, the WFH recognizes that existing therapies have their limitations. “Product innovation is an important part of meeting the global supply.”

The WFH is working on a number of initiatives:

- **Very rare bleeding disorders:** Because the population of patients who have FV, FVII, FXI, and FXIII deficiency and do not have hemophilia or von Willebrand disease (vWD) is so small (10,500 patients have been identified), running clinical trials is difficult. This situation makes it very difficult to meet the challenges of bringing products to the market.
- **Unused plasma proteins:** As countries have made the transition to recombinant products, some cryoprecipitate unused for the production of FVIII and FIX concentrates has gone to waste. Because of the vision of executive committee member Mr. David Page, the WFH has been working to bring partners together to stimulate the development and use of this product to benefit others around the world. A pilot project in Canada is working on developing affordable clotting factor concentrates that might be used to support humanitarian aid and access needs in emerging countries.
- **Regulatory harmonization:** The influence of key regulatory bodies—specifically, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA)—is paramount. These agencies drive much of what happens around the world and by specifying differences that don’t make sense from a safety or efficacy perspective, they can negatively influence access, cost, and portability of products between countries.
- **Twin-track pricing:** Following innovative WHO pricing models related to access to therapies and vaccines for the human immunodeficiency virus (HIV), the WFH is exploring the possibility pricing systems that would allow products to be more affordably sold to meet needs in emerging countries—for example, by offloading investment and development costs.
- **Von Willebrand disease:** The WFH is incorporating vWD into its new strategic plan, with the goal of improving diagnosis and access to treatment options for the estimated 43,000 people with vWD around the world.

Mr. Skinner encouraged participants to have a candid exchange of perspectives so that they can together find solutions for affordable supply and stimulate the development of products and the pursuit of new avenues for treatment.

Theme: The use of factor concentration

Dose and Outcome in Hemophilia Care

Dr. Alok Srivastava, Christian Medical College, Vellore, India

The management of hemophilia involves preventing bleeding and arthropathy, maintaining full musculoskeletal functioning, and more recently, maintaining quality of life, said Dr. Alok Srivastava. Clotting factor concentrates play a very important role in the treatment of hemophilia. In the 20th century, longevity for people with hemophilia increased significantly when clotting factor concentrates were introduced—and when viral transmissions occurred with those concentrates in the 1980s, longevity was also affected.

Dr. Srivastava presented data showing that, in countries with more clotting factor concentrates, people with hemophilia have a longer life expectancy. Data from Sweden for 1992 show that increased quantities of clotting factor concentrates could almost completely prevent joint disease and maintain normal joint function and architecture. These data became the basis for the current hemophilia management paradigm, which involves starting treatment before one year of age and providing primary prophylaxis and maintaining a regimen of fairly large doses thrice weekly for patients with hemophilia A and twice weekly for patients with hemophilia B. The aim is to maintain a factor level above 1% at all times. This regimen requires the use of a large quantity of concentrates—3 to 8 IU per capita—at considerable cost.

Although this model is successful, said Dr. Srivastava, the issue of optimum dose arises because, all over the world, there are demands on resources and competing health care needs. Compliance and convenience are also important issues, especially with regard to children. Moreover, there may be side effects with intensive doses. A study in 2004 showed that the use of clotting factor concentrates has risen to between 6 and 7 IU per capita from between 2 and 4 IU per capita, he reported. This increase comes with enormous cost implications, and raises the question of whether increasing the dose to that level is really necessary. “Do those costs justify the effects, or are there more efficient and cost-effective ways for treatment? Should we be trying to prevent every joint bleed, or do a certain number not matter to the overall outcome,” Dr. Srivastava asked. Efficiency and cost benefit are not just preoccupations of the developing world, he added.

The use of clotting factor concentrates for both prophylaxis and on-demand treatment has gone up in last three decades, with better outcomes for joint disease. However, said Dr. Srivastava, a question remains: How do outcomes, measured in terms of bleeds per year and radiologic score, translate in terms of quality of life for patients? Data from the Netherlands, which used lower, “intermediate” prophylaxis levels of clotting factor concentrates achieved similar radiologic scores at nearly half the dose, he noted. Data from India and Brazil show similar radiologic scores even with much lower doses. Long-term data on the outcomes of various doses in terms of quality of life are lacking, he said. “We need to develop methods to assess overall function rather than just joint scores.”

Two observational studies are under way. One, which is being conducted in nine developing countries, is looking at dose and its impact on long-term musculoskeletal function. Another is looking prospectively at the varying dosages and outcomes of patients in Sweden and the Netherlands.

The limitations of current paradigms include

- A clinical score that has an unclear correlation with overall musculoskeletal function.
- The low sensitivity and significance of the radiologic score (which has been acknowledged to be poor)
- A lack of known advantages for the magnetic resonance imaging scale.

Moreover, quality of life tends to be affected not only by musculoskeletal function, but also by psychosocial issues and economic status.

Since the end of the 1990s, the WFH has been developing a performance-based function assessment. There is a remarkable paucity of data related to optimum dosage, said Dr. Srivastava. Dr. Carol Kasper's data from the mid-1980s remains the largest study on surgery and hemophilia.

Dosage protocol has become much higher without much evidence, Dr. Srivastava said. An increase in the mean dose to 2000 IU/kg in the 1980s from 600 IU/kg in the 1970s was not associated with a change in bleeding complications. Dosage needs are similar in developing and developed countries, but doses vary. "We still don't know the optimum dosage for surgical prophylaxis in hemophilia—which has led to wide variation in practice," said Dr. Srivastava. Is a minor hemorrhage that does not affect outcome acceptable? Depending on the answer, significant differences can be seen in the doses used.

"Hemostatic level" may be defined as the lowest plasma concentration of a given coagulation factor that is required for normal hemostasis. There are data that suggest that lower doses may be sufficient for hemostasis. Early studies showed efficacy in controlling joint hemorrhage even with lower doses. In some countries, diagnoses of bleeding disorders are not perfect, and people with factor levels of 10% to 15% have been taken through major surgeries without major problems. Data from thrombin generation assays show near-normal responses at factor levels of 30%.

For many situations, data are lacking, but guidelines are still required for practice, Dr. Srivastava noted. Guidelines help national programs to plan for expenditures. They also serve as an educational tool for health care providers unfamiliar with hemophilia management. "The principles of managing this condition all over the world are the same," said Dr. Srivastava. "It is shown that if you do not have significant resource constraints, you can follow conventional dosage today. On the other hand, if you do have significant resource constraints, you can follow what in some situations has been shown to be reasonably safe."

The doses used really depend on the evidence, the resources available in a country, the definition of endpoints (for example, whether a minimal number of bleeds is acceptable), and social expectations. "What's happening now is that large parts of the world are using very low doses as a practical measure, and some parts are using the maximum doses possible. We need to determine what is optimum, and [to] define what is practical," said Dr. Srivastava. Currently, 40% of the world uses less than 2% of the global supply of factor concentrates. How can hemophilia be managed more cost-effectively? A shift is needed in the way that the outcomes of various doses are documented and the way in which outcomes are measured—particularly in terms of musculoskeletal function and quality of life, Dr. Srivastava concluded.

Discussion

Dosage is not the only aspect of hemophilia that lacks a significant evidence base, a participant said. This participant noted that the actual characteristics of the patient population—lifestyle, weight, physical activities, socio-economic status, and so on—are seldom specified in regard to dosage. He wholeheartedly agreed on the importance of not overdoing the dose. Beyond the issue of inhibitor development, big pathogen problems occurred in the 1970s and 1980s, he reminded the audience. The most-affected segment of the population included those who had been most exposed to the products. In case of future problems, dosages need to be very carefully scrutinized. This participant added that, at the start of his career in the 1980s, “one unit per head was nirvana.... Now we’re pushing six and eight—the target is always a moving target.” It is timely and appropriate to call for a structure and a ceiling for dosages, he said.

Dr. Srivastava agreed that dose levels have risen since the mid-1990s. He reiterated that the optimum level needs to be determined—something that is particularly important for certain emerging countries.

Regarding getting factors up to 100%, a participant noted that, in dentistry, extraction of a single tooth is now being done with an international normalized ratio of 4. And, despite the fact that a normal platelet count is 150 to 400, the practice is to go down to 50% in dentistry—100% is not needed. In terms of prophylaxis, nurses in hemophilia centres need education about improving the oral hygiene of their patients; such improvements will in turn reduce the amount of treatment the patients need and their exposure to products. Dr. Christine Randall in the United Kingdom has published findings.

Another participant said that developed and developing countries can learn much from each other. A lot of work that has been done in developed countries with the conviction of having achieved a “gold standard” may be erroneous.

Yet another participant noted that, from a patient perspective, there is considerable variability in treatment even in the same country. Efforts to develop an optimum dose and management guidelines also need to take into account individual variation. There may not be just one optimum number, this participant said.

Extensive scientific research into the dosage issue is critical, offered another participant, noting that health authorities would pounce on opportunities to reduce budgets for the immense economic load of hemophilia care.

One participant noted that there are ways to potentiate prophylaxis, citing the prophylactic effect of physiotherapy. Prophylaxis is not just about factor concentrate, she said.

There are great variations in practices and needs around world; perhaps an optimal dose should be determined by geographic area, a participant suggested.

Gathering and publishing data about dosage is extremely important, a participant emphasized. The optimal dosage may not be possible in most countries; data are needed about the dose required for function and independence at an affordable cost for people in developing countries.

A participant mentioned how difficult it can be to collect data on the quantity of factor being used, especially for prophylaxis. This difficulty is the focus of a pilot project related to inhibitors. The project is developing a methodology for simpler and more accurate data collection, he said.

The “gold standard” seems to be associated with economic development in each country, a participant observed. A “gold standard” could have dangerous implications.

Another participant said that the “gold standard” should be based on good quality of life and the absence of joint problems, rather than on dose.

A participant mentioned the importance of taking into account the prophylactic benefits of physical activity.

Emerging countries are looking to the international experience of dosage and cost, and are seeking data from international clinical studies, a participant said. The WFH could play a key role in developing international protocols.

Trends in the Plasma-Derived and Recombinant Markets—Clinician’s Perspective

Dr. P.M. Mannucci, A. Bianchi Bonomi Hemophilia and Thrombosis Centre, Milan, Italy

At the Third WFH Global Forum in Budapest, Hungary, in 2003, polling results showed a feeling among participants that the availability of products is of foremost importance (48%) and that supply and safety are important (26%), said Dr. P.M. Mannucci. Availability is the more cogent issue in developing countries, and safety the more cogent one in developed countries, he added.

Since the early 1990s, more and more people with hemophilia have been treated with plasma-derived or recombinant products. Enhanced production of these products has facilitated access, including in developing countries. Worldwide demand for and use of both plasma-derived and recombinant FVIII concentrate have increased dramatically since the early 1990s, particularly because of the introduction of recombinant FVIII. The availability of recombinant FVIII in turn increased the overall quantity of FVIII available to hemophilia A patients.

Recombinant concentrate represents 42% of the quantity of FVIII available to patients. Most of it (88%) is used in North America and Europe. Europe shows large consumption of plasma-derived factor. Some recombinant product (12%) is used in Asia, mainly in Japan. However, in other countries, consumption of recombinant products is practically negligible. Plasma-derived products tend to be used extensively in the developing world.

During the same 15-year period, the availability of plasma-derived factors also climbed as a result of increased fractionation. Plasma-derived FVIII is increasingly used in emerging markets, with its use growing exponentially in South America, the Middle East, and Asian and Pacific countries.

The issue of safety involves not just pathogens but, more pressingly, inhibitors. The gloomy story of the 1980s and 1990s—a period when a great number of people with hemophilia became infected with hepatitis C and HIV through pooling of plasma—has been considerably ameliorated. With the advent of highly active retroviral therapies, both diseases can be controlled.

The introduction of desmopressin acetate (DDAVP) in Italy in the late 1970s was critical to protecting people with hemophilia in that country from infection with HIV. But DDAVP did not become available in the United States until around 1985, said Dr. Mannucci. In Italy, patients have a 2% HIV prevalence as compared with 18% in patients with mild hemophilia in the United States, he reported. Surveillance for HIV among people

with bleeding disorders in the United States has shown no seroconversion to anti-HIV in 71 hemophilia treatment centres (HTCs), and the same is true for hepatitis B and C. DDAVP is an efficient treatment, said Dr. Mannucci. However, it remains to be seen whether DDAVP will become widely available in developing countries.

Evidence suggests that plasma-derived products are much safer than in the past. In fact, they are very safe. For example, there has been no documentation of prion transmission by plasma-derived products, and fractionation has a good capacity to remove prions. Nonetheless, recent experience shows that pathogens will continue to emerge and re-emerge. Safety surveillance should not be diminished, said Dr. Mannucci.

Dr. Mannucci reported that new data for FVIII inhibitors demonstrate that patients who were previously anti-titre and who were treated with plasma-derived products showed a lower cumulative incidence of inhibitors than did patients treated with recombinant products. As well, preliminary data from retrospective studies indicate that previously untreated patients that received large amounts of vWD factor showed a lower incidence of inhibitor risk. He also suggested that switching patients from one product to another is not a good practice, because use of multiple products may be linked to a higher incidence of inhibitor development than is use of single products.

Trends in the Plasma-Derived and Recombinant Markets—Regulator’s Perspective

Prof. Albert Farrugia, Head, Blood and Tissues Unit, Australian Therapeutic Goods Administration

Recombinant products clearly have a much higher level of potential control and therefore safety than do plasma-derived therapies, said Prof. Albert Farrugia. The latter products still depend on pooling of factors from a large number of donors. However, Prof. Farrugia emphasized that plasma-derived products will remain important to hemophilia therapies for the foreseeable future.

The plasma industry is changing dramatically, Prof. Farrugia said—expressing some reservation and apprehension. The resulting consolidation and fast-shrinking number of players in the market is remarkable. The danger is that no single company has the capacity to generate all the products, especially those for niche markets. In addition, having a vibrant competitive tension between the various players is important for encouraging competition on safety enhancements.

Factor concentrates from pharmaceutical manufacturers are subject to manufacturing and quality control processes that are similar for plasma-derived and recombinant products alike. In fact, the plasma industry may be the most regulated of the pharmaceutical sector, said Prof. Farrugia. This is appropriate, he indicated; but, at the same time, the level of regulation influences access.

Regulatory agencies exist to demonstrate and assure that products are safe and effective, and of high quality. They use a number of tools to do this job—licensing of manufacturing facilities, pre-market product assessment, and post-market surveillance, for example. The clinical trials for plasma and recombinant products are similar.

The features that contribute to safety and quality are extremely necessary, Prof. Farrugia emphasized. In addition to being subject to regulatory processes, manufacturers and industry conduct their own safety audits. A deficiency in any of these processes compromises quality. Good manufacturing practices are critical. The range of approaches to the manufacture of FVIII and FIX concentrates results in significant differences in products

and in the purity of products. It is important to individually assess the problems with various products, rather than to extrapolate, Prof. Farrugia said. Facility licensure is a way to ensure good manufacturing practices.

Internationally, however, and unlike the situation in most areas of pharmaceutical practice, plasma is not subject to adequate and appropriate levels of harmonization in terms of regulatory oversight. Three different routes are pursued in the European Union:

- **Centralized procedure:** Mandatory for recombinant products and some plasma-derived products
- **Mutual recognition procedure:** Used to acquire authorization for “older” technology products
- **National procedure:** Authorization in a single country

Comparing the EU and FDA approaches, Prof. Farrugia noted that the FDA considers recombinant products to be “well-characterized proteins,” justifying a lighter regulatory touch. On the other hand, the EMEA requires recombinant products go through the centralized procedure and a higher level of evaluation. A high level of review is essential, Prof. Farrugia said. Pharmacokinetic data are important, but efficacy studies using the same design are essential.

Inhibitor risk is currently the foremost safety issue for regulators. Pathogens are an issue of the past for plasma-derived and recombinant products alike, he suggested; however, continued vigilance is needed for both types of product.

Treatments for Rare Disorders (U.S. Initiatives)

Dr. Donna DiMichele, Special Coagulation Research Laboratory, New York Presbyterian Hospital - Weill Medical College of Cornell University, Food and Drug Administration, United States

When it comes to rare bleeding disorders, the United States—like most of the rest of world—is very much an emerging market, said Dr. Donna DiMichele. Dr. DiMichele’s talk addressed issues related to rare bleeding disorders, including deficiencies of FII, FVII, FX, FV, FXIII, and fibrinogen and the dysfibrinogenemias.

The objectives of the North American Rare Bleeding Disorders Registry, which originated in the late 1990s, are to collect prevalence and epidemiology (including phenotype) data, to characterize the type and severity of bleeding manifestations, to assess treatment strategies being used in North American hemophilia treatment centres, and to document complications of these diseases and their treatments.

A survey of HTCs in Canada and the United States drew a response rate of 26%. The survey identified more than 8000 patients of various ages with rare bleeding disorders. Bleeding is the most frequent diagnostic event, followed by family history and preoperative laboratory work. The skin and mucus membrane are the sites most likely to be involved in bleeding. Among the more severe rare bleeding disorders, musculoskeletal bleeding is also a significant issue. Disease-related complications and their rate of occurrence were quite variable among individual patients.

Early work found that the treatment used most often for rare bleeding disorders was fresh-frozen plasma (FFP) and cryoprecipitate, with activated prothrombin concentrates for vitamin K-dependent patients. Various treatment-related complications occurred, including some allergic reactions with the heavy use of plasma-derived products.

An issue that the North American Rare Bleeding Disorders Registry brought to light was that FVII is one of the more frequent of rare bleeding disorders. But at that time, neither FVII plasma concentrate nor recombinant factor was available in the United States. “Our situation [lagged] behind those of other countries,” Dr. DiMichele said.

Registries and databases are important for identifying cases and patients for future clinical trials, she said. New clinical trial designs are needed because traditional designs can no longer be applied to these patients and products, she added. Substantial interest in harmonizing data collection exists.

A forum is needed to discuss the varying data needs of regulators, industry, physicians, and consumer organizations. Voluntary post-marketing surveillance must be distinguished from post-marketing surveillance that monitors patients to assure the accuracy of reports, said Dr. DiMichele.

It is also important to consider developing an alternate, harmonized regulatory pathway to examine the potential of international market authorization based on similar clinical trial criteria. Other potential opportunities are available to improve investment analysis for industry (for example, developing “small indication” grants or taking advantage of “orphan drug” financial incentives) and to examine regulatory options such as discussion of product development for rare plasma protein disorders.

The priority, said Dr. DiMichele, should be to establish an international database that amalgamates existing databases documenting the distribution of patients affected by rare bleeding disorders and the available treatments and barriers to therapies. This database should also help to provide evidence-based guidelines for the diagnosis and management of patients. For the FDA, harmonizing its instruments with international instruments in a priority, she added. Dr. DiMichele reiterated that a new approach is needed to get products for rare bleeding disorders to market.

Treatments for Rare Disorders (European Registry)

Dr. Paula Bolton-Maggs, Manchester Royal Infirmary, United Kingdom

The 2004 U.K.-produced guidelines for the treatment and management of rare bleeding disorders was based on available evidence, most of which came from case reports or small series, said Dr. Paula Bolton-Maggs; little evidence was available from randomized controlled trials. Even if evidence is insufficient, guidelines can be put together based on current best practices. They can be revised when evidence becomes available, she noted.

The United Kingdom has been at forefront of national data collection: the registry on rare bleeding disorders has been in place since 1968. All hemophilia centres annually report information on their patients, treatment modalities and levels, and other pertinent information.

Differences can be seen in the types of disorders affecting various populations in different parts of world. In India, the frequency of Glanzmann’s thrombasthenia is 40% higher than in the United Kingdom; India also lacks the predominance of disorders of FVII seen in the United States and the United Kingdom. Dr. Bolton-Maggs also noted that diagnosis and treatment of platelet disorders is even more complicated than that of rare bleeding disorders.

Even in developed countries, discrepancies in the availability of treatment for rare bleeding disorders can be found, she noted. For example, preliminary data from the North American and European registries show that hardly any treatment was administered in the United States, but that, in Europe, a variety of plasma products – and in some cases, recombinant products – were administered.

Most of rare bleeding disorders are inherited; they are much more common in areas of world where marriage between cousins is common. Generally, rare disorders present a less clear correlation between bleeding and factor levels, making management more difficult.

A range of products is manufactured for treating rare bleeding disorders. No concentrate is available for FV deficiency, and so that disorder is treated with virus-inactivated FFP. In the United Kingdom, Octaplas from pooled sources and methylene blue-treated single-donor units are also options. For platelet disorders, treatment options include DDAVP, fibrinolysis inhibitors, platelet transfusions, and recombinant FVIIa. Fibrinogen treatment products are also available, but these virus-inactivated concentrates are unlicensed. Finally, cryoprecipitate is a good source, but it is not virus-inactivated.

A variety of options are available for FXI deficiency. Bio Products Laboratory (BPL) recently released a FXI product that had been held up because of thrombotic risk—showing the importance of post-market surveillance to detect complications.

The international project initiated in 2004 is very exciting, said Dr. Bolton-Maggs. Preliminary data show a varying distribution of deficiencies across different countries. FXI deficiency is more common in northern Europe. In Central and South America, more FVII deficiency is seen. In North America, access to plasma concentrates is almost nonexistent because of licensing. Access varies in different parts of the world. International collaboration is key to improving diagnosis and management of rare bleeding disorders, she concluded.

Discussion

Dr. Giangrande stated that the WFH position is quite clear: plasma-derived and recombinant factor concentrate are preferred to cryoprecipitate, but there is no preference between the former two options—the choice is up to patients and their caregivers.

From the viewpoint of regulators and clinicians, the safety aspects of recombinant and plasma-derived factor may really be related to the perception of risk and risk management instead of safety, a participant suggested.

Dr. Mannucci replied that very careful surveys show highly isolated reports of blood-borne infection because of accidents long in the past. The record of recombinant products is immaculate, he added. The main issue is prion transmission—and so far, despite preoccupations in the United Kingdom, no evidence of transmission by blood products has been seen. For the time being, evidence of safety is good; but the picture changes when it comes to pathogens and inhibitors.

Prof. Farrugia pointed out that plasma-derived and recombinant products are licensed and on the market because both have been approved by regulators. Approval means that both products are considered by regulators to be safe and to have a place in hemophilia treatment. In Australia, recombinant product is treated with less concern than plasma-derived product is. However, he added, governments and regulators must be extremely sensitive to perception; experience has shown that one person's perception can be another's reality.

The data about lowered inhibitor risk with vW factor are compelling, one participant said. Can recommendations be made about using vW factor for initiation of treatment in previously untreated children?

Dr. Mannucci said that the evidence is compelling, but still insufficient. Even some of the best studies have limits. The retrospective studies provide evidence for plasma-derived products, but ethnicity, genotype risk, quantity, and age are not controlled. The ideal would be to conduct a randomized controlled trial, but that approach is impossible: perception would cause it to be judged unethical by some patients.

Dr. Mannucci said that he is considering a prospective study in countries in which only plasma-derived product is available. However, it is important not to appear to be passing risk on to others while recommending recombinant product. Therefore, the study would be ethical only in a country in which only plasma-derived product is available. “If we follow the same procedure as for the licensing of recombinant products, we would have at least good historical control.” One challenge will be controlling for the quantity of factor to be administered. The hope is that, with the help of industry, it will be possible to provide product free of charge.

Emerging countries cannot afford primary prophylaxis with recombinant product; they can afford only prophylaxis with plasma-derived concentrates, a participant said. What is the advice for countries whose primary prophylaxis involves factor concentrate?

Prof. Farrugia said that prophylaxis regimes are possible with both recombinant and plasma-derived products. The use of both could be advantageous from the viewpoint of being able to assess inhibitors from the two products. Dr. Giangrande said that ensuring the availability of sufficient factor in a given country for on-demand treatment, and then for prophylaxis, is key.

Regulation exists to ensure that products on the market are safe to the level that science demands, Prof. Farrugia said. In Europe and the United States, products on the market are as safe as they can be. Emerging pathogens are a theoretical risk for recombinant products, and the fractionation of plasma-derived products is effective. Variant Creutzfeldt-Jakob disease (vCJD) is, however, another issue.

Dr. Mannucci noted that virus inactivation methods are effective in removing emerging pathogens except for prions. Inactivation methods are very efficient, he said. Because recombinant and plasma-derived products are both biologic products, an absolute minimum risk exists for both, he added. However, perception is important.

From a scientific viewpoint, rare bleeding disorders have known treatments, and plasma can be purified to make products. Why, then, are so few products available—even decreasing in availability? Is regulatory pressure making it hard to produce products economically?

Prof. Farrugia said that he has been concerned to learn that the Laboratory for Fractionation and Biotechnology (LFB) in France is stepping back from producing FVII concentrate. This change is not attributable to regulatory pressure, because most of the concentrate is delivered through special-access provisions. However, assembling the kind of data pack required for standard licensure is very difficult because of clinical trial issues. Nevertheless, Prof. Farrugia said that he believes that manufacturers should be able to provide more clinical data—but obtaining that data just isn’t economical. This situation leads to great apprehension about problems with FXIII and FXI, and with products for other rare bleeding disorders, which are also delivered through special-access provision. Dr. DiMichele observed that the clamour for quality of care and for products is not same for rare bleeding disorders as for hemophilia, which has had the benefit of substantial physician and patient advocacy. As well, many products can easily be made available through plasma-derived factors. But as recombinant technology emerged, the plasma

industry was hesitant about the direction in which to go with investment in plasma-derived products. Dr. DiMichele also noted that licensure requirements for these products have never been reviewed in a novel way that acknowledges insufficient subjects for clinical trials according to classical clinical trial design. International harmonization is key, she said. The source material and technology for products exist, but regulatory requirements for clinical trials in various countries have been a tremendous barrier.

Prof. Farrugia reiterated that regulators are not stopping products (particularly FXIII) for rare bleeding disorders from coming to market – but it is up to the companies to provide data.

When clinical data are insufficient, effective virus-inactivation processes and post-licensing surveillance should be considered satisfactory criteria for moving forward with treatments for rare bleeding disorders; otherwise, products will never get licensed, said Dr. Mannucci.

Regarding the development of databases, a participant asked whether clinicians would be ready and willing to collaborate by enrolling patients who would remain anonymous into clinical trials. Difficulty in recruiting patients remains a key impediment, said this participant.

Dr. DiMichele replied that both patients and physicians are ready.

Prof. Farrugia asked for comment on whether FVII concentrates were removed from the market recently because of regulatory constraints or lack of profitability.

“Both,” replied a representative from LFB in France. Plasma-derived FVII was definitely challenged by the regulatory position on state-of-the-art coagulation factor using double inactivation. FVII concentrates from LFB were subject only to single inactivation. “This investment, compared to residual market, is unfortunately not matching our resources,” he said.

Dr. Srivastava suggested that, if creating individual products for individual deficiencies is difficult, prothrombin complex concentrates (PCCs) might be used to at least cover FVII and FX deficiencies.

Room exists for tremendous creative thinking about cost-effective solutions, and PCCs warrant consideration, said Dr. DiMichele. Dose, dose efficacy, and safety are the most critically important data, she said – noting that, when a product with multiple clotting factors is used, fine-tuning the dose efficacy and safety profile becomes more challenging.

Theme: Supply, safety, innovations, and emerging issues

Mr. David Page, Chair, Safety, Availability and Supply Committee, WFH, introduced the session, noting that the first speakers would discuss harvesting unused proteins from plasma fractions. “Although we’re talking about innovation, many issues are a return to the past,” he noted.

Unused Proteins from Plasma Fractions

Dr. Thierry Burnouf, Human Plasma Product Services, Lille, France

Dr. Thierry Burnouf began by noting that the WFH is encouraging plasma fractionators and collectors to develop new ways to exploit plasma or fractions that are currently unused. To address this issue, it is necessary to determine the quantity and type of unused plasma available and the possible limitations to its exploitation.

The available unused plasma comes mostly from whole-blood donations, Dr. Burnouf said. Of the roughly 16 million litres of plasma collected annually worldwide, 3 million litres are used for transfusion, leaving 13 million litres for fractionation. Approximately half of this 13 million litres is actually fractionated, mostly in developed countries. Part of what remains is used to make cryoprecipitate and blood bank plasma.

Most of the excess plasma comes from fragmented collection centres in developing countries, Dr. Burnouf noted. These centres tend to lack coordinated blood transfusion systems, and they yield small quantities per centre. In general, the resulting plasma does not meet the quality standards for fractionation, and the national regulatory authorities (NRAs) in the countries of origin lack the experience necessary to regulate plasma or plasma-derived products.

This situation suggests that the focus should be on unused industrial cryoprecipitate. However, in developed countries (with the exception of Canada), no unused cryoprecipitate is available. What is not used by a particular fractionator is generally sold to other producers.

Some interesting circumstances in China might yield surplus cryoprecipitate for fractionation, Dr. Burnouf said. Currently in that country, more than 5 million litres of plasma are fractionated annually, but the driving protein is albumin; very little FVIII or IX is produced. In fact, less than 10% of the available cryoprecipitate is used for FVIII, leaving 4.5 million litres available.

FIX is less of an issue, Dr. Burnouf said, because it can be made from cryo-poor plasma and because the clinical need is lower and recovery is double that for FVIII. However, cryo-poor plasma and FIX intermediates are both liquid. They are therefore more difficult to transport.

Dr. Burnouf outlined several challenges associated with the use of plasma and plasma intermediates. Most of the available material does not meet the quality criteria of fractionators or NRAs for testing, freezing, and storage conditions. Significant regulatory work would be required to qualify this plasma as a source for medicinal products. The cost and quantity of the source material, plus the manufacturing costs, must yield a return on sales, which requires economies of scale.

In some countries, legal issues may prohibit exports of cryoprecipitate. Other legal issues include liability for product side effects (including pathogen transmission) and technology licensing issues. Some countries may lack freeze-drying capacity or the equipment for cold plasma thawing or cryoprecipitation.

In conclusion, Dr. Burnouf reiterated that unused recovered or recoverable plasma is available in developing countries. In addition, some other countries have unused cryoprecipitate potentially available. But before these resources can be utilized, the technical expertise of local NRAs and plasma producers has to be boosted.

Collector's Perspective

Dr. Graham Sher, CEO, Canadian Blood Services

Dr. Graham Sher began by outlining the background of Canadian Blood Services (CBS) and by identifying some recent trends. In 2004–2005, half of the CBS budget was spent on plasma protein product costs. Recombinant products accounted for 42% of plasma protein costs, and product utilization has continued to increase for most products. Dr. Sher called the growth in FVIIa and intravenous immune globulin (IVIG) consumption “alarming.”

CBS and its sister organization Héma-Québec send 190,000 litres of plasma to Talecris annually for fractionation into IVIG and albumin, Dr. Sher said. This transfer fills one quarter of the total Canadian need; product for the other three quarters is purchased on the commercial market.

Dr. Sher outlined several other relevant trends:

- Increased use of recombinant FVIII and FIX have reduced revenue from plasma-derived clotting factors.
- Plasma collection has been scaled back. (Throughput has been reduced by 3 million litres per year.)
- Concentration and consolidation in the industry continue.
- The American Red Cross has stopped contract fractionation.

Canada is a small market (it accounts for just 4% of global sales for IVIG, for example), but security of supply is a major concern, Dr. Sher said. Cognizant of this fact, CBS initiated a plasma protein products strategic plan in 2003. This plan parallels the entire supply chain from collection to warehousing. One of the interesting shifts in the plan is a movement away from self-sufficiency as a goal. Instead, the plan has set a target of providing for 40% of domestic needs from Canadian plasma.

One of the other issues handled by the strategic plan is that of surplus proteins. Last year, Canada shipped 192,000 litres of recovered plasma for fractionation, said Dr. Sher. However, in the near future, Canada intends to switch to the buffy coat production method, and the impact that this switch may have on cryoprecipitate characteristics and yield is unclear.

With respect to Canada's commitment to explore the use of recovered plasma for the extraction of FVIII and other proteins, discussions are underway with the National BioProducts Institute (NBI) in South Africa and with the WFH. Dr. Sher described the potential project with NBI as “ambitious,” and emphasized that CBS is still examining legal, liability, consent, and ethical issues, technical and manufacturing questions, costs, and plasma collection constraints. However, he emphasized that CBS is committed to exploring all options to support the initiative.

Fractionator's Perspective

Mr. Duncan Armstrong, Executive Director, National BioProducts Institute, South Africa

Mr. Duncan Armstrong began his presentation by providing some background on the current NBI initiative aimed at enhancing the availability of affordable plasma-derived products. The initiative takes advantage of unused donated proteins. He emphasized that this project is not the only one that may make plasma products more available, but that it could be used as a model. Other efforts might focus on lengthening the shelf life of donated products and on enhanced systems for delivering humanitarian donations of products.

The potential source material is from CBS, Héma-Québec, and the Australian Red Cross Blood Service, Mr. Armstrong explained. Discussions are also underway with Bayer, CSL (formerly Commonwealth Serum Laboratories), and NBI regarding the possibilities of using intermediates such as cryo and cryo-poor plasma for the production of FIX. It will be necessary to conduct facility audits and to ensure that regulatory requirements for the quality of plasma and intermediates are met.

Mr. Armstrong said that it was “fortuitous” that NBI was already in the process of upgrading its facilities to increase capacity. With the upgrade projected for completion by 2006, “the timing is perfect for this project.” The upgrade will provide additional capacity, but the quantity and quality of the cryo, which is directly related to fill volume, may still be a constraint. Currently, NBI produces intermediate-purity, solvent-detergent-treated FVIII and solvent-detergent-treated FIX prothrombin complex. These products can be stored at room temperature to accommodate their many clients who lack refrigeration.

Both inbound and outbound regulatory considerations apply, said Mr. Armstrong. These include:

- Approval of all materials by the Medicines Control Council, which can take from six to nine months.
- Audit reports on plasma sources and intermediate processing centres.
- The need to ensure that local and destination requirements are met and that products are registered and import permits granted.
- The acquisition of export permits from the South African Department of Health.

Determining how the product will be distributed could be a sensitive issue. “Although we are a not-for-profit organization,” said Mr. Armstrong, “we understand the dynamics of the market.”

Decisions regarding distribution will be handled by collaboration between the WFH, WHO, the South African Health Authority, CBS, Héma-Québec, and NBI. The focus will be on providing product to countries in southern Africa and to other developing countries.

Product would be provided on a cost-recovery basis, he said. Because NBI already has the manufacturing capacity and technology agreement partnerships, and because source material (the largest single cost in production) will be donated, it should be possible to provide products inexpensively. Funding will be provided on a joint basis. “The real challenge is to provide free products, because in a country that has no money, even cheap products are inaccessible.”

Mr. Armstrong concluded by emphasizing that this program can succeed and overcome its challenges through collaborations and partnerships, while continuing its commitment to the patient as its Number 1 priority.

Better, Safer Cryo: Is It Possible, Is It Cheaper?

Dr. Gail Rock, Editor-in-Chief, Journal of Transfusion and Apheresis Science

Dr. Gail Rock called the renewed interest in cryo “intriguing.” She noted that most of the available data are more than twenty years old, but that they still offered possibilities for the future. “Certainly, it’s possible to make better cryo. Over the years, we’ve identified more than twenty variables in terms of optimizing cryo.” These factors include donor blood type, time to freeze or thaw, rate of freeze or thaw, temperature, and anticoagulant. Also well established is the fact that plasma stored below -40°C will stay potent for years.

Dr. Rock noted that, during the first 24 hours after donation, FVIII activity decreases by 50%; however, after that, it becomes relatively stable. Also, FVIII levels in whole blood are not much different at 22°C and at 4°C . “Buffy coat” production requires material to be held for 24 hours before processing, which results in a 50% yield reduction in FVIII. But most fractionators seem to accept this as a reasonable trade-off, Dr. Rock said.

The process for making cryo is simple. Plasma is frozen, thawed, and then centrifuged; the cryo is then removed. However, this process is totally reversible; it is important to remember that, if cryo is left standing in plasma, even at 4°C , the material will return to solution in its entirety.

A number of important and innovative discoveries have been made. The thaw-siphon technique has enhanced FVIII yield, and a number of additives have also been used to improve the yield.

In the 1970s, CaCl_2 was used to split FVIII from vWF (von Willebrand factor). It’s now known that calcium is an integral part of the FVIII molecule; removing it causes instability, said Dr. Rock. The next advance, she explained, was to improve the yield of FVIII using heparinized plasma. Further research has shown that adding decreasing amounts of citrate (until heparin is present alone, with no calcium) leads to increased effectiveness of FVIII plasma. Yields were enhanced because of the ability to preserve low-molecular-weight FVIII. FVIII stored in heparinized plasma is also more stable. Studies also showed that FVIII recovery increased from 50% in citrated plasma to 78% in heparinized plasma. In addition to increasing cryoprecipitability, adding heparin to plasma allows for a cold insoluble-globulin purification step, Dr. Rock said.

Dr. Rock cautioned about the difficulties in conducting clotting assays, but she concluded that making a better cryo is possible. However, the economics will vary from country to country.

Plasma Standards and Yield

Prof. Albert Farrugia, Head, Blood and Tissues Unit, Australian Therapeutic Goods Administration

Prof. Albert Farrugia reviewed several of the regulatory requirements regarding plasma. In Europe, two sets of standards are available: a monograph in the European Pharmacopoeia and a chapter on plasma for transfusion in the Council of Europe Guide. In the United States, the only codified requirements are for plasma for derivatives manufacture.

Prof. Farrugia noted that regulatory requirements – particularly those regarding the freezing and storage of plasma – are predicated on the need to preserve FVIII. A good case can still be made for optimizing FVIII preservation, because – being the most labile therapeutic

protein—it is a good marker for overall plasma quality. The marked differences in European plasma standards indicate how difficulties arise when the same material is used for two completely different reasons—notably fractionation and transfusion.

Prof. Farrugia outlined several of the considerations that influence FVIII yield, particularly those that depend on the collection and manufacturing processes.

The normal practice when blood is collected is to immediately chill it and to keep it refrigerated to minimize bacterial growth. These conditions are inimical to FVIII preservation, although FVIII can actually be recovered again if the blood is warmed.

One of the most important logistics issues in terms of plasma processing is the time to freezing. Delaying the time until plasma is frozen to a core temperature results in lower FVIII levels. In general, delay affects the cryo yield and, sometimes, the low- and intermediate-purity concentrates. No data are yet available for the current generation of FVIII concentrates.

Prof. Farrugia said that significant ambiguity exists across the various standards for freezing rates, and that much variation exists concerning the appropriate freezing state. The important issue is not the ultimate temperature, but the speed with which that temperature is attained. Empirical evidence suggests that freezing to -30°C within 30 minutes results in higher FVIII yields. Slower freezing also results in increased fibrinogens.

As long as the plasma is frozen quickly, storage temperature does not seem to matter. Temperatures from -20°C to -40°C are equally good, but it is important that the storage temperature remain stable.

Prof. Farrugia cautioned that there are some indications that plasma that has not been well processed can have effects on product quality. Many patients using a particular high-purity plasma-derived FVIII product manufactured during 1993–1995 developed inhibitors. The reasons for this occurrence are still somewhat unclear, but further study is warranted, he said.

Prof. Farrugia also reminded participants that FVIII is not the only protein harvestable from plasma and that the presence of heparin could have implications for other products.

Prof. Farrugia concluded by emphasizing the need for clear and unambiguous standards—particularly those concerning the minimization of microbial contamination—that will result in consistent products. However, some issues (such as FVIII yield) should be left to manufacturers and suppliers to decide, as long as those decisions do not affect quality.

Discussion

A participant asked whether regulatory authorities would consider cryoprecipitate from heparinized plasma to be a blood bank product or a pharmaceutical.

Prof. Farrugia said that the distinctions between cold fractionated products are made on the basis of pool size. FFP is considered a component. Solvent-detergent-washed product is considered a medicinal product. To be considered a pharmaceutical product, it must be derived from a pool of 50 or more donors.

Mr. Skinner asked Dr. Rock if it would be possible to create a full-scale program, modeled on the improved cryo possibilities that she had presented, that could provide a safe,

reliable production system in an emerging market. Dr. Rock replied that there is nothing particularly “high-tech” about the process. If riboflavin techniques come to fruition, it should be possible to deal with extremely small batches.

Several participants had questions regarding the effect that the switch to buffy coat production in Canada would have. Dr. Sher said that CBS will use the buffy coat method to extract platelets from whole blood, leaving recovered plasma to make cryoprecipitate for the treatment of rare bleeding disorders. He also noted that current data suggest that using the buffy coat method will result in lower, but still acceptable, levels of coagulation factor recovery.

Dr. Bruce Evatt said that one of the biggest obstacles to improving care in developing countries is the belief that cryo is adequate for people with hemophilia in their communities. Concentrates can be made for ten to fifteen cents per unit, only slightly higher than cryo. Given that cryo complicates treatment by requiring refrigeration and by posing other administrative issues, it seems unjustified to use cryo except in cases in which nothing else is available. He emphasized that cryo is an inferior product. “It saves lives, but we end up with individuals who are crippled by their teens.”

Dr. Rock replied that cryo is being used today, and so everything possible should be done to make it better.

Dr. Burnouf suggested that concentrates cannot actually be produced for such a low cost. They can be offered less expensively in some markets because of the high prices (forty to fifty cents per unit) charged in other markets.

Dr. Mannucci said that he was not convinced that virus inactivation is possible without unreasonably reducing yield.

Prof. Farrugia noted that any inactivation or purification process will result in loss of yield. If the product that is being generated is being further refined, a process with a high yield will be required. Although the price differential between products may not end up being large, there are still countries in which people are dying because they have no access to product at all.

An industry representative noted that industry listens carefully to what patients are saying. A plea for therapies for rare bleeding disorders is being made, and industry is more inclined to make that investment.

Potency Labelling of FVIII and FIX Concentrates: Regulatory Harmonization?

Dr. Trevor Barrowcliffe, Head, Division of Haematology, National Institute for Biological Standards and Control, Potters Bar, United Kingdom

Dr. Trevor Barrowcliffe urged participants to consider the issue of potency labelling from the viewpoints of various stakeholders, including manufacturers, regulators, accountants, clinicians, and patients.

There are currently three different ways of labelling, Dr. Barrowcliffe explained. Most of Europe uses nominal value. In the United States, the actual assay value is listed on the vial. Recently, the United Kingdom has required dual labelling, although not on recombinant products.

Manufacturers tend to prefer nominal value labelling, said Dr. Barrowcliffe. Such labelling is easier and provides a clear target for production. Regulators like it because it makes licensing easier. It also makes accounting more straightforward. Patients and clinicians alike find dosage calculations simpler.

On the negative side, however, manufacturers must allow for batch and assay variability. Consumers may be paying for higher dosages than they actually receive, and the uncertainty of content could lead to uncertainty in dosing. That uncertainty in turn encourages product wastage through overdosing, Dr. Barrowcliffe said. With nominal labelling, target overshooting may result in less product availability. Undershooting creates more product, but possibly with less efficacy per dose.

With actual labelling, the manufacturer is fully paid for each unit in the batch, and patients and doctors can be more certain of the dose. On the other hand, regulators can find it difficult to write licenses.

Dual labelling, on the other hand, allows for more transparency, said Dr. Barrowcliffe. Regulators then have a good check on the accuracy of the nominal value, and accountants, patients, and treaters know that “what they see is what they get.”

Dr. Barrowcliffe noted that assay precision seems to have improved in recent years. Few laboratories surveyed in 2003 showed a coefficient of variation (CV) greater than 10%. Dr. Barrowcliffe also presented data from a study by the National Institute for Biological Standards and Control. This study conducted by Dr. Sanj Raut looked at the actual potency of several FVIII products. The CV between assays was as much as 20% for some products. The B-domain deleted recombinant product tested was actually 15% below nominal potency.

In conclusion, Dr. Barrowcliffe posed several questions for consideration:

- Could U.S. concentrates with actual potency labelling be accepted in Europe without re-labelling?
- Is $\pm 20\%$ still an appropriate limit for FVIII assay precision?
- Should products with average potency within 85% of nominal still be acceptable?
- Could dual labelling be accepted in all countries?

Re-labelling (Re-validation)

Dr. Johannes Dodt, Paul Ehrlich Institute, Germany

Because of their biologic nature, blood products are inherently variable, said Dr. Johannes Dodt. Therefore, a set of strategies and agreed principles are required to ensure quality, safety, and efficacy. These strategies and principles must ensure

- Quality starting material.
- Control of the manufacturing process.
- Product compliance and standardization of methods for testing.
- Adherence to good manufacturing practices.

Specifications for biologic medicinal products are product-specific. They are also linked to analytical procedures, manufacturing processes, product stability, and clinical studies, said Dr. Dodt. The key point is validation of the manufacturing process to ensure that operations fall within established parameters. Ultimately, specifications and validation

processes are used to establish marketing authorization (MA), which is the model for ensuring that products are of suitable quality, known safety, and efficacy.

In finished-product testing, potency (with respect to degradation during storage) is the most sensitive parameter for FVIII. The European Pharmacopoeia requires 80% to 120% of nominal potency; the FDA requires 80% to 120% of initial potency.

Dr. Dodt said that, in his experience, finished-product tests for viral markers are not conclusive because they yield so many false positives. Other methods such as donor screening and exclusion, nucleic acid amplification testing (NAT), and validation of virus inactivation during manufacture are more effective.

Shelf-life is “the period of time a medicinal product is known to stay within acceptable specifications under defined storage conditions.” Each blood product has its own unique stability characteristics, so that shelf-life is based on long-term, real-time, real-condition stability studies, plus studies conducted under accelerated and stress conditions.

Re-labelling would involve assigning a new potency to a product batch at or near its expiry date. The activity or safety profile of a particular product does not undergo a sudden change on its expiry date, but no further knowledge about stability, safety, or efficacy is available.

Re-validation, said Dr. Dodt, would involve re-labelling under certain validating conditions. This process would require a product to be retested at the end of its shelf-life. A new set of shelf-life specifications would be assigned. This process would create more knowledge about the behaviour of the product.

Neither re-labelling nor revalidation is consistent with MA. Dr. Dodt suggested that these practices should be allowed only on a case-by-case basis and only when need for a product is urgent. Even then, it is still unclear who takes responsibility and assumes the risk for re-labelled or revalidated products.

The Case for Global Collaboration in Studies on Inhibitors in Hemophilia

Dr. Mike Soucie, Division of Hereditary Blood Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, United States

Dr. Mike Soucie began his presentation by reviewing recent studies that have established a cumulative rate of inhibitors in previously untreated patients of 25% to 32% (which eventually fell to 12%). In previously treated patients, studies indicated a rate of 1% to 3% over two or more years—mostly in low-titer patients with fewer clinical symptoms than in the more common higher-titer previously untreated patients. Dr. Soucie also reviewed many of the risk factors that are thought to be related to inhibitor development, including intron 22 gene inversions, large gene deletions, family history, race, mutations in other immune response genes, and early exposure to coagulating factors.

Several elements pose challenges to inhibitor research:

- It is methodologically difficult to characterize and to perform risk assessments for rare adverse events.
- Evaluation of treatment product risk uses a probabilistic model that most patients find unsatisfactory.
- Current clinical trial methodology is problematic, because sample sizes are not adequate to assess risk, and randomization to the larger population is difficult.

Dr. Soucie then described the Universal Data Collection Program currently in place in the United States. It uses a national protocol to collect uniform surveillance data from patients at 135 HTCs. More than 90% of eligible patients have given informed consent to participate in the study, which has an enrolment of more than 11,000 patients. Although the study was not set up to study inhibitors, it does collect data that may be related, including demographic information, bleeding frequency (to measure exposure), inhibitor test results, and all product brands used since the last visit.

To test the feasibility of monitoring inhibitor incidence, a group of frequent HTC users was studied, said Dr. Soucie. Among the 838 patients studied, nine new verified inhibitor cases occurred, for an overall rate of 2.75 cases per thousand patient-years. Rates varied from 6.78 with Monoclate P to 1.66 with Kogenate. The study indicated that the incidence of inhibitors in previously treated patients is very low. However, despite nearly four years of follow-up, the study was not able to detect differences in rates between levels of risk factors or to adequately assess differences in rates between products.

The most feasible way to study the “rare adverse event” is through post-marketing surveillance of a large population, Dr. Soucie concluded. To that end, the Centers for Disease Control (CDC) has designed a pilot study of post-market surveillance for inhibitors. Ten HTCs have been selected for the pilot; each will enrol 50 patients. Inhibitor testing and hemophilia gene testing will be done at the CDC. Hopefully, said Dr. Soucie, this type of large-population monitoring will be sufficiently powerful to examine a rare event such as inhibitors. To obtain data adequate to identify risk factors and assess product risk, he concluded, international collaboration will be required.

A New, High-Yielding Affinity Cascade for Sequential Isolation of Plasma Proteins of Therapeutic Value

Dr. Christopher Bryant, Project Manager, Plasma Protein Purification System

Dr. Christopher Bryant pointed out that nearly 80% of people with hemophilia remain untreated. That proportion rises to 94% when people have immunodeficiency and 97% when they have alpha-1 deficiencies. To address the global treatment gap, increased manufacturing capacity through new plants, increased yields from new or improved processes, and the introduction of new products and applications are required. However, the yield of FVIII from plasma fractionation continues to be only 5% to 10%.

To address these realities, said Dr. Bryant, the Plasma Protein Purification System (PPPS) was initiated as a joint project between ProMetic Life Sciences Inc. and the American Red Cross. The objective is to develop a high-efficiency production platform for manufacturing plasma-derived therapeutic proteins. More specifically, the project will use affinity chromatography to recover the most important therapeutic proteins with better yields than those currently obtained, while promoting safety, reliability, and cost-effectiveness.

The system is a sequence of affinity chromatographic adsorption steps, using synthetic ligands specifically designed for maximum binding with particular target proteins, Dr. Bryant explained. Although seven plasma proteins were initially targeted, the sequences can be adapted to specific needs, and steps can be omitted if a protein is not needed. Virus reduction technology takes place downstream.

Essentially, the process is a cascade, he explained. The plasma (which has not been cryoprecipitated) is loaded onto a column. vWF/FVIII is derived directly by adsorption onto an affinity resin designed to attract it. Then, a similar process occurs for plasminogen, fibrinogen, immunoglobulin G, albumin, and alpha-1 proteinase inhibitor (A1PI).

The yields of the seven target proteins have been extremely good, ranging from 60% for vWF/FVIII to 90% for A1PI, Dr. Bryant said. In terms of economics, higher in-process yields mean higher product yields and increased purity, which may reduce the number of downstream purification steps and create a potential for reduced operating costs.

Some of the other considerations that may reduce production costs include a lower plasma requirement for equivalent product yield, a processing temperature of 25°C (rather than -5°C), more highly automated systems, and the elimination of the ethanol-recovery infrastructure.

Another important part of the system's development has been to ensure mechanisms for robust technology transfer. PPPS can therefore be a partner in bringing the technology forward, Dr. Bryant concluded.

Update on Bayer Research and Development Initiatives

Dr. Bernard Chiasson, Director of Scientific Development, Bayer Healthcare, Biological Products, Canada

In research and development, said Dr. Bernard Chiasson, one starts with a pathology, and progresses along the path to a cure. In hemophilia treatment today, most people are familiar with a number of options, but some interesting future options are on the horizon. These include a product with an extended half-life that requires fewer treatments, orally-dosed treatments, and a possible gene treatment, which would effectively be a cure.

Initial mouse studies of Bay 79-4980 (Kogenate FS-Pegylated Liposome Diluent) suggest normal recovery with a prolonged residency time, especially in the terminal phase. The formulation of recombinant FVIII with pegylated liposomes results in specific, high-affinity, non-covalent binding, which does not inhibit interaction with vWF or FVIII, Dr. Chiasson explained. Bayer has received permission to undertake a phase I trial and has a projected a product launch date of 2009.

Dr. Chiasson then presented an update on Next Generation Kogenate (KGN). The aim of the project has been to extend the period of action of FVIII. Three approaches to enhance activity are being used: activity muteins, binding muteins, and pegylated muteins. To date, the in vitro data with activity and binding muteins has been very promising, but in vivo studies have been less so. Pegylation results suggest improved recovery in hemophilic mice, but the data are still preliminary.

Other current research is focused on the development of gene therapy treatment for FIX, said Dr. Chiasson. Although previous attempts at gene therapy have been failures, Bayer continues to be committed to the idea that gene therapy is a potential curative strategy. In this case, FIX is an ideal target: the gene is small and it codes for a stable protein with high potency, but requires low expression levels. The concept has been proven in animal trials, particularly in dogs, which have maintained FIX expression for years in studies.

Dr. Chiasson concluded by emphasizing Bayer's continued commitment to investment and strategies for the improvement of the treatment and prevention of factor deficiency.

Discussion

Dr. Soucie was asked several questions about possible ways to filter or interpret the UDC (Universal Data Collection Program) data on inhibitor patients. He noted that a number of analyses of the data had already occurred, but that too few cases are available yet to demonstrate anything beyond the fact that too few cases are available.

Dr. Mannucci asked if it might not be more efficacious to use the UDC data to tackle the issue of differential immunogenicity of plasma-derived versus recombinant products in previously treated patients, than to conduct another study on inhibitors in those patients.

Dr. Soucie explained that the proposed study would be on all patients, not just previously treated patients. Because the approach is surveillance, rather than a clinical trial, it will allow large numbers of patients to be involved, and large amounts of risk data to be acquired without great expense. He expressed his hope that other countries might be able to provide data similar enough to provide a subject base large enough for comprehensive study.

Dr. Evatt and others underscored the usefulness of collecting comprehensive global surveillance data on inhibitors. Dr. Mannucci agreed, saying he that was making an overt offer to model the European surveillance system in such a way as to make it compatible with the UDC.

Dr. DiMichele asked if PPPS would be adaptable to other rare protein disorders such as deficiencies of FV and vitamin K. Dr. Bryant said the possibility exists of going after any protein that has therapeutic value.

Mr. Skinner noted that, as a humanitarian agency, WFH collects donations and often runs into problems with expiry dates. He asked if it would be possible for regulatory authorities to develop a template for countries that might be willing to accept product beyond the normal MA, so that they can be helped to evaluate on a case-by-case basis.

A participant replied that it should be possible to evaluate data available at marketing authorization and for other countries to set new specification and new shelf life. Although opportunities for co-operation exist, it's important that countries take the necessary steps to accommodate the process.

Dr. Bryant said that the real question is, "What's magic about eighty per cent?"

Dr. Barrowcliffe said that FVIII is very stable; the difficult thing is coming up with a shelf-life in the first place. For a lot of product, the actual shelf life could be extremely long; the process of actually determining shelf-life is extremely imprecise.

Day 2: September 27, 2005

Update on Safety Issues (TSEs and inhibitors)

Mr. Mark Skinner, President, World Federation of Hemophilia

The arrival of variant Creutzfeldt-Jakob Disease has raised issues of risk assessment and risk analysis related both to vCJD and to risk communication with divergent populations, said Mr. Mark Skinner, who moderated this session. Participants would hear about experiences and perspectives on risk assessment in the United States, Canada, and the United Kingdom.

Risk Assessments for Plasma Product Recipients: The Case of Imported FXI in the United States

Dr. Mark Weinstein, Food and Drug Administration, United States

In September 2004, U.K. authorities notified people with bleeding disorders and anti-thrombin III (ATIII) deficiencies that they might be at increased risk of vCJD from plasma derivatives that they had taken. The plasma derivatives at issue had been manufactured in the United Kingdom from plasma donors in the United Kingdom and had been distributed during 1980–2001, said Dr. Mark Weinstein.

The U.K. notification was motivated by increased concern about transmission of vCJD after two individuals had apparently acquired vCJD from transfusions of a plasma donation from a patient with vCJD. The material was a non-leukocyte-reduced red-blood-cell preparation, not a plasma derivative, said Dr. Weinstein, but it illustrated that blood has the potential to transmit vCJD. Recommendations from the U.K. authorities were to notify all patients who received coagulation ATIII products; to advise them to refrain from donating blood, tissues, and organs; to inform surgeons and dentists of their increased risk; and to inform families so that, in emergencies, healthcare providers could be told of potential risk.

In the United States, a few patients deficient in FXI were treated with FXI concentrate made in the United States from U.K. plasma from 1989 to 2000 under investigational new drug (IND) protocols. FXI deficiency is a very rare plasma disorder affecting between 1 in 30,000 and 1 in 1 million people. The deficiency produces variable bleeding tendencies that usually manifest during surgery. The population of patients and caregivers was immediately identifiable through IND.

Dr. Weinstein then described an FDA risk assessment model of the potential of FXI product to transmit vCJD. The model was developed by Dr. Steve Anderson of the FDA. The model presented an estimate of the reduction of clearance of the prion in the manufacturing process; the most likely level is one log removal of material from the product. However, estimates ranged from no clearance to four logs of clearance, and great uncertainty was undoubtedly present, Dr. Weinstein noted. Another uncertainty is whether different routes of administration (intracranially or intravenously) made a difference in efficiency.

The model estimates that a patient receiving 15,000 U of FXI has an average potential risk of approximately 1 in 7 (with a probability range between 1 in 200 and 1 in 2) of being infected with vCJD. However, Dr. Weinstein said the risk assessment is highly uncertain and may even be inaccurate, because how the results from the animal experiments that

were used in the risk assessment apply to humans is unknown. Moreover, some individuals infected with the vCJD agent may never become ill with the disease. Finally, no direct studies of vCJD clearance by manufacturing processes have been undertaken.

The FDA intends to notify patients about potential risk by using letters to recommend to IND sponsors that they contact patients. Direct contact between physician and patient should then occur so that the patient receives an explanation about their potential to acquire the disease from the particular product. This information will be included in the letter and will be posted on the Internet.

Implications of vCJD Risk Assessments for Patients and the Need for Open and Transparent Communication

Mr. David Page, Canadian Hemophilia Society

Risk assessment and communication regarding vCJD and plasma products is very challenging given the huge levels of uncertainty surrounding the issue, said Mr. David Page. For patients, information and clarity are lacking. A precautionary approach is recommended when scientific knowledge is incomplete.

The September 2004 communication to patients in United Kingdom specified a 1% or greater risk of being exposed to vCJD through FVIII products. In Canada, it was known that about 50 patients had received FXI products up to 2001 (the products had been prescribed under a special-access program). It was possible to contact the physicians and patients quickly, but the issue was what to communicate. Health Canada had conducted its own risk assessment and concluded that the risk was between 1 in 100,000 and 1 in 1 million—a wide range, noted Mr. Page. Nonetheless, using the same products from same donors given in same quantities, the Canadian analysis came to different conclusions, and Health Canada recommended that no extra infection control to be taken. Thus, two different messages were sent from the two countries to their patient populations, Mr. Page said.

The consequences in the United Kingdom were that, after September 2004, some people were refused access to basic dental care and surgery. In addition, public health authorities provided no compensation to hospitals for equipment destroyed as a precautionary measure.

Notification varied immensely. In the United Kingdom, letters were sent to embassies of countries that had imported implicated batches of clotting factor concentrates. However, the batch numbers of implicated products or a list of countries that had imported the products between 1980 and 2001 was not released. WFH collected information from member countries and published that information on its website.

In Canada, no evidence of the embassy route being effective, nor of information reaching CBS, Héma-Quebec, or public health agencies was seen, Mr. Page said. Do not all patients have the same right to be notified of a suspected health risk? Should not government and manufacturers notify health care professionals and patients who have used implicated products? A comprehensive global notification requirement for donor plasma may help to ensure that foreigners and nationals are treated equally.

Discussion

The U.K. notification was issued with short notice and no proper consultation with expert physicians in field, Dr. Giangrande said. Patients have suffered discrimination in the context of certain procedures, but many of the initial problems have now been resolved. One requirement in his own hospital is to label all blood samples from people who have hemophilia and who received plasma products “at risk.” Hemophilia professionals are seeking to reverse that requirement. Things are getting better, but there still some problems, Dr. Giangrande said.

A big problem nationally is that sterilization of medical and dental instruments is extremely poor, a health care professional said.

No study describes the clearance of prions from FXI concentrates, Prof. Farrugia noted. He said that risk assessments and outputs depend strongly on three assumptions, some of which are quite challengeable. Canadian input is based on observed clinical manifestation of disease; the FDA and Australian assessments make a different presumption: presumption of carrier state. This approach, although unfortunate in the outcomes it produces, is scientifically more valid, Prof. Farrugia said. He also said that the communication by the British authorities in September 2004 was deplorable.

Mr. Skinner emphasized the continued importance of risk communication.

Theme: Affordability of factor concentrates

National Tender Systems—An Overview

Mr. Brian O'Mahony, Irish Haemophilia Society

Developing a tender process involves deciding who will be the contracting authorities to purchase the product, and then establishing a tender commission, the composition of which is extremely important, said Mr. Brian O'Mahony. A tender commission must include leading clinicians and representatives from the National haemophilia Organisation.

The tender process involves determining whether the tender falls within the remit of the commission- products, thresholds, and product type (plasma-derived, recombinant, or both). Tender procedures can follow national procurement rules or EU directives on tenders (compulsory for EU countries).

There are different types of tender processes. The most commonly used procedure is an open tender where the tender is advertised and all companies are invited to submit tenders. In restricted tenders, specific elements of design or of intellectual input are required, and particular firms are invited to tender. In competitive tenders, a minimum of three companies are pre-qualified and invited to bid. A negotiated tender is used in exceptional circumstances when only one possible supplier is available.

Selection criteria are crucial, Mr. O'Mahony emphasized. These criteria can include price, most economically advantageous tender, and diversity of suppliers. It would be a major concern if clotting factor concentrates were chosen solely on price, he said. Price is one factor, but safety, efficacy, quality and supply considerations are also key. Only products that meet minimum standards should be considered.

Scores and weighting factors are assigned to each criterion, and the tenders are rated on score sheets. It is important to note the rationale behind the scores, both for the record and in case of challenges. Decisions should be communicated without delay.

The term of tender can vary from three months to three years, said Mr. O'Mahony. His preference is for a two-year tender, because a lot of product development can occur in three years.

Between tenders, keeping up with developments in the area is extremely important; the commission must maintain its level of knowledge about products, must gather reports on product use and adverse effects, and must keep abreast of trends and developments. The formal involvement of leading clinicians and representatives from HTCs is vital, he added.

National Tender Systems—An Industry Perspective

Mr. Jan Bult, President, Plasma Proteins Therapeutics Association

The PPTA strongly supports freedom of choice, patient access to care, open-market principles, and regulatory oversight, said Mr. Jan Bult. The PPTA opposes restriction of choice, preferred-drug lists, sole-vendor contracts, and restriction based on price. "A tender is against all these principles, but sometimes it is the only option available."

Another disadvantage of tenders is that no guarantee is given of a consistent supply at the end of the contract, Mr. Bult said. Moreover, when countries change suppliers, the patient population needs to be put on another therapy. A focus solely on price may result in the purchase of low-quality products.

Open markets are the best way to avoid compromising quality and safety, he emphasized—fair game and fair treatment.

Tendering—The U.K. Experience

Dr. Paula Bolton-Maggs, Manchester Royal Infirmary, United Kingdom

Since 1998, the U.K. government has made funding available for recombinant products for all children under 16 years of age with hemophilia. In 2003, coverage was extended to adults, said Dr. Paula Bolton-Maggs. The Department of Health has been working out a strategy with HTCs and local health systems to transfer patients to recombinant products in phases.

A critical principle is that clinicians continue to have prescribing freedom, said Dr. Bolton-Maggs. HTCs usually discuss their annual volumes individually with companies and then negotiate a price. This process disadvantages smaller centres, though. Centres find that it is also important to have several sources of supply.

A working group determined that, to get best possible price and consistency across the country, a national tender should be placed for the products. Information from the National Hemophilia Database helped to determine the precise number of patients with severe hemophilia and the quantity of products used from April 2002 to March 2003. The assessment of likely volumes took into account both anticipated use and indicative prices from the drug companies. It was decided that each primary care trust would receive a sum allocated according to the number of patients and the agreed product. The process would be audited quarterly.

The national agency for purchase and supplies issued an invitation to tender to the official journal of the European Community. Four companies were involved; they were asked to tender for sample volumes varying from 10% to 60% of the U.K. supply. Industry representatives were interviewed by a tendering subgroup. Two companies came up with volume-linked prices one third below the usual, said Dr. Bolton-Maggs. Clinicians were shown the offers and asked to place their orders, which would be reimbursed.

In the first year, 528 patients were funded. The following year, 568 patients received funding. However, problems included a shortfall between volume commitments and volumes actually purchased, possibly because some patients had product remaining from the previous year. Most HTCs are now dealing with two contracts, one based on the previous price and one on the recombinant rollout, Dr. Bolton-Maggs explained. However, it is not clear whether the government will maintain the current tendering system in the future.

Case Study—Brazil

Dr. Suely Rezende, Haematology Specialist and Advisor to the Brazilian Ministry of Health

Dr. Suely Rezende described the purchase and distribution of factor concentrates in Brazil, where about 6300 people are known to have hemophilia A or B. Treatment is largely based on demand; home therapy, primary prophylaxis, and immunotolerance are not available. The use of cryoprecipitate has been banned since 2002, and within the last two years,

patients have received highly purified factor concentrates purchased by the Ministry of Health at a cost of about US\$100 million annually. Brazil does not have the technology to produce factor concentrates, and so all products are either imported or fractionated by industry. Recombinant products are not purchased, except for small amounts of recombinant FVIIa.

A seven-member technical committee, including the president of Brazilian hemophilia society, academics, and hematologists working in HTCs, oversees tendering. The committee is responsible for designing the technical specifications, which are normally approved by the head of coordination of Blood and Blood Products, a division of the Ministry of Health. The tender specifications then pass through the financial division before being announced publicly on the ministry Web site and in newspapers. The tender process takes place two to four times annually, which is a bit much, said Dr. Rezende. The technical committee revisits the specifications once each year and makes revisions when necessary.

Technical criteria involve double- or single-inactivation FVIII and FIX concentrates and a nanofiltration removal step. The criteria is a well-priced product, but one that meets the technical specifications, said Dr. Rezende. Brazil's process involves "upside-down bidding," in which the winner is the lowest-priced product that meets the technical specifications. Savings of up to 60% over the previous price have been achieved, she said.

The process is more transparent and economical; however, it is also very time-consuming and bureaucratic. Also, changing products brings added risks, she concluded.

Discussion

Prof. Farrugia asked the panel to comment on the issue of continual changes of product. "There is growing perception that it is good to keep patients on a single product as much as possible. The more product that is available the better," he said.

Dr. Bolton-Maggs agreed that basic principle of treatment is not to change products unless necessary. "Will there be a ripple of inhibitors with patients transferring from plasma to recombinant," she asked. It is better to remain with a single product unless significant improvements become available, she suggested.

Mr. O'Mahony said that concerns regarding continual switching of products have been explored, but no evidence that such switching increases inhibitors is available. He also observed that, although the industry may look at restrictions based on price as a disadvantage, "it's the reality of the world. It's unrealistic to expect the government of a country not to pick the lowest-priced products. Restriction based on price is just economics." This increased the importance of ensuring that leading clinicians and haemophilia organisation representatives were involved in the tender process-to ensure that only products which met the required standards of safety, efficacy and quality were considered on the basis of cost.

Mr. Bult noted that double inactivation is more expensive, but also safer. Restrictions based on price produce different standards of quality, force hospitals to opt for the cheapest products, and force patients to change therapies, he added.

A participant asked if Brazil had looked into using recovered plasma thrown away in Brazil. Brazil is trying to launch its own fractionation plant and is in the process of arranging for transfer of technology, this participant was told.

A participant asked Mr. O'Mahony how the tender process complicates donations to the national patient organization when that organization sits on the tendering commission. Mr. O'Mahony replied that the Irish organization has suspended directed donations from companies since the introduction of the tender process. "Perception is just as important as reality, and openness and transparency are critical."

The tendering system in Australia follows a philosophy that sees safety as the domain of the regulator. If the regulator passes a product, it is safe, a participant said.

Prof. Farrugia recommended that the modus operandi should be to maintain a number of players and a multiplicity of suppliers.

A participant suggested that, to reduce inhibitor risk, a precautionary principle on not changing therapies should be developed. He also wondered if central procurement for patients already being treated could be established, with tendering only for products for untreated patients.

National surveillance in the United Kingdom shows no clear evidence at the moment that switching therapies increases inhibitor risk, Dr. Bolton-Maggs noted.

The situation from the perspective of patients could be said to be rosy: prices are down and supply is up, a participant said. At the same time, this participant called attention to the warning from the influenza vaccine sector about the result on the availability of vaccines of the significant consolidation since the mid-1990s. Ratcheting down can be good in the short term, but in the long term, manufacturers will not be there for rare coagulation disorders and vWD factors, the participant warned.

Price Usage and Variation

Mr. Mark Brooker, Public Policy Officer, World Federation of Hemophilia

Mr. Mark Brooker reported on data that the WFH has compiled from its global survey, which collects information from clinicians and health professionals through local member organizations. In last year's survey, demographic information about patient populations, blood-borne infection, and access to treatment products, health care systems, and the use of factor concentrates was collected from 96 countries, representing about 85% of the world population.

The survey identified 120,812 people with hemophilia A and B, 43,334 with von Willebrand disease, and 11,384 with other bleeding disorders.

Mr. Brooker cautioned that the survey figures were not independently verified and that data quality may vary. Figures for "total annual usage" may not accurately reflect actual annual usage, given that some countries may purchase products outside of national tenders and that some sources may go unreported.

Based on reports from 49 countries, the total consumption of FVIII concentrates was 1.5 billion IU. In countries in which the per capita gross national product (GNP) was greater than US\$10,000, FVIII usage was 5.32 IU per capita. Where per capita GNP was between US\$2000 and US\$10,000, usage was 0.75 IU per capita.

Total reported use of FIX was nearly 237 million IU. Per capita usage was 0.72 IU in the richest countries, 0.13 IU in the intermediate countries, and 0.02 IU in countries in which the per capita GNP was less than US\$2000.

Mr. Brooker also presented data on purchasing prices for 17 different products, adjusted for purchasing power parity (PPP) which reflects what it means to pay for a product, not the profit that manufacturers make:

Beriate	Hemofil M AHF	Octanate
Aventis Behring	Baxter	Octapharma
Price US \$0.19–\$0.82 PPP US \$0.29–\$0.87	Price US \$0.20–\$1.08 PPP US \$0.33–\$1.08	Price US \$0.16–\$0.94 PPP US \$0.25–\$1.08
Fanhdi	Immunate	Recombinate
Grifols	Baxter	Baxter
Price US \$0.39–\$0.96 PPP US \$0.60–\$0.87	Price US \$0.18–\$0.96 PPP US \$0.29–\$0.85	Price US \$0.64–\$1.51 PPP US \$0.66–\$1.23
Haemate	Koate DVI	ReFacto
Aventis Behring	Bayer	Wyeth
Price US \$0.29–\$1.46 PPP US \$0.53–\$1.66	Price US \$0.14–\$0.68 PPP US \$0.35–\$0.68	Price US \$0.41–\$1.13 PPP US \$0.61–\$0.98
Helixate	Kogenate	
Aventis Behring	Bayer	
Price US \$0.79–\$1.21 PPP US \$0.67–\$1.08	Price US \$0.56–\$1.36 PPP US \$0.61–\$1.81	

The lowest price for FVIII products varied widely from US\$0.14 to US\$1.80. A similar range was observed for the variety of FIX products (from US\$0.17 to US\$1.75). Median prices ranged from US\$0.60 to US\$1.00 for FVIII. Mr. Brooker noted that the range of prices for some products—such as Kogenate—was wide. However, an examination of product prices adjusted for PPP revealed that the range was not as large as it appeared when the exchange rate alone was used.

Mr. Brooker said that the survey found that plasma-derived FIX products were less expensive than recombinant versions, but not by much.

In finishing his presentation, Mr. Brooker noted that not many truly firm conclusions can be drawn from the data beyond the facts that the price paid covers a broad range and that using PPP narrows that range. Even using PPP, the cost of the products in the developing world is significantly higher as a proportion of per capita income.

Increasing the Worldwide Supply of Safe, Affordable Factor Replacement Therapy: Differential Pricing

Dr. Neelam Dhingra, Coordinator, Blood Transfusion Safety, World Health Organization, Geneva

Dr. Neelam Dhingra presented information from the WHO Database on Blood Safety to demonstrate how differential pricing affects the affordability of factor concentrates and the safe supply of products. The total annual blood collection in 178 countries is 81 million litres, she said. However, 60% of that supply is available only to the 20% of the world's population in the developed world.

The WHO blood safety mission is this:

To contribute to the improvement of blood transfusion safety in Members States.

Many considerations affect access to medicines, Dr. Dhingra said. These include rational selection and drug use, adequate financing, and reliable supply systems. "Price is only one factor, but an important one – especially in developing countries."

In developed countries, drug costs are largely publicly funded through insurance or reimbursement plans, said Dr. Dhingra. However, in the developing world, patients pay for 50% to 95% of drugs by themselves. This situation increases the impact that prices have on access.

Dr. Dhingra outlined several approaches being used to reduce the prices of medications:

- Differential (tiered) pricing, whereby prices are adjusted to reflect purchasing power at their destinations
- Competition between suppliers (including research-based and generic manufacturers)
- Regional and sub-regional procurements (purchasing with larger volume discounts)
- Licensing agreements that allow developing countries to produce medicines of the same quality at lower costs
- Parallel importation, whereby products are bought in countries in which licensing arrangements have set lower prices and then are exported to other countries
- New funding mechanisms from the public and private sector to help pay for treatment

Dr. Dhingra outlined the details of the Agreement on Trade-related Aspects of Intellectual Property Rights, which improves access by differential pricing, depending on national ability to pay. "International intellectual property rights are an instrument of public policy, but international rights of the person should take precedence over property rights," she said.

Dr. Dhingra presented two case studies of situations in which WHO played a crucial role in reducing the price of vaccines or treatment. These initiatives were country-driven, with various UN agencies providing technical support. One project – for the procurement of antiretroviral drugs – saw WHO assist 19 countries to reach agreements with manufacturers for the provision of lower-priced medicines. In the second case, a vaccine procurement arrangement allowed low-income countries to purchase vaccines more cheaply as the result of a WHO/UNICEF bulk procurement. "These successful cases provide grounds to initiate debate on which mechanisms could be utilized to make factor concentrates less expensive in developing countries," Dr. Dhingra concluded.

Facilitating Humanitarian Donations: WFH Program

Ms. Claudia Black, Program Director, World Federation of Hemophilia

Dr. Assad Haffar, Humanitarian Aid Coordinator, World Federation of Hemophilia

Ms. Claudia Black explained that the WFH humanitarian aid program aims to increase global access to treatment. The program started in 1996. It channels donated clotting factor concentrates to people with hemophilia in severe need in countries with limited access to treatment.

Ms. Black said that the program meets immediate short-term needs, but also provides support and hope, and in addition, assists other projects through initiatives such as twinning. Humanitarian aid can also have long-term impacts because product donation can provide the leverage necessary to spur the implementation of national hemophilia treatment programs.

Dr. Assad Haffar highlighted several cases in which the provision of humanitarian aid had had a significant impact. These included the case of an Afghani child who was a refugee in Iran and who needed life-saving surgery, a summer camp in Argentina made possible by the provision of donated factor concentrate, and support given to help establish good donation practices in the Philippines through GAP.

One of the major challenges, said Dr. Haffar, is that WFH can't control donations, and it is simply not possible to project or predict supply. The program is overseen by four regional program coordinators who do the groundwork necessary for the humanitarian and other WFH programs.

The WFH humanitarian program is the largest and most credible supply channel for donated hemophilia treatment products, said Dr. Haffar. Last year, donations were channeled to more than 17,000 people in 55 countries.

Ms. Black explained that the WFH accepts regulator-approved products from manufacturers, hospitals, and homecare companies. The products must have a minimum of two months' shelf life remaining, although the ideal is six months. Donations are repackaged at Hemophilia of Georgia or at WFH headquarters in Montreal. Products are then shipped to recipients who have been chosen based on expressed and confirmed need. WFH ensures that the products are shipped to registered HTC's or to national member organizations.

Ms. Black outlined several of the challenges facing the humanitarian aid program. These include the constant need for donations, international security concerns, limited shelf life of the products, the unique nature of clotting factor concentrates, and the necessity of finding ways to avoid wasting the potentially life-saving products.

Discussion

A participant said that, in his experience, products were still excellent six months after their expiry date, even if some of the potency is lost. He called the waste of any potentially life-saving product "outrageous," and urged WHO to change its margin for donated products from one year of remaining shelf life to six months past the expiry date. His organization is considering hiring objective technicians to evaluate the safety and potency of expired products. He also noted that other donation programs exist outside of WFH. For example, Israel provides donated products directly to the Palestinian Authority.

Dr. Barrowcliffe said that the whole issue of determining expiry dates with regard to potency is very imprecise. Clotting factor concentrates are freeze-dried products. If they're properly stored, they're likely safe, and determining the potency is not difficult. The expiry date alone should therefore not be a deterrent to use of the product.

Dr. Giangrande noted that the WFH is particularly in need of donated FIX and of products for patients with inhibitors.

Another participant expressed concern that differential pricing could lead to products migrating back into higher-priced markets through "unofficial channels."

Dr. Dhingra said that WHO is very careful to ensure that products purchased for developing countries don't end up in richer markets. She emphasized the need for vigilance and monitoring.

The WFH was asked to publish the results of the product price survey on its Web site and to update it annually. Mr. Brooker said that the presentation would be posted, but he expressed some trepidation about posting all of the survey results because of concerns regarding the quality of the data. However, the WFH will provide the information to any member nation upon request, he said.

Several participants emphasized the importance of collecting hard data about product potency and activity level beyond expiry. It was recommended that WFH, or some of its members, institute a procedure for re-validation.

Prof. Farrugia emphasized that shelf life is just one part of a whole nexus of arrangements that provide quality assurance for factor concentrates. Although it is necessary to make product available in emergencies, he advised caution and emphasized the importance of a transparent process with rigorous standards.

Mr. O'Mahony pointed out that the WHO shelf-life regulations for donated product were designed to ensure that unsafe drugs didn't get dumped on developing countries. The difficulty is in coming up with appropriate guidelines for hemophilia treatment products, which are different from most other pharmaceuticals. He also noted that countries purchased and re-validated products during the recent global product shortage. It may not be worth re-validating small donations, but larger ones might justify a more comprehensive re-validation process.

Dr. Dhingra said that one of the reasons WHO has set the shelf-life limit at one year is the lack of a good distribution system in many countries. It might be worthwhile to consider products with shorter shelf lives while focusing on improving delivery and distribution systems.

Mr. O'Mahony noted that WFH sends products only to countries with well-established distribution systems.

The WHO program for improving blood safety and supply in developing countries is most important, another participant said. Product donation may be a short-term solution, but the medium-term and long-term solutions require that self-sufficiency be improved in developing countries.

Dr. Dhingra noted that WHO has several mechanisms in place to improve safety and supply. These include the promotion of nationally-coordinated blood transfusion programs, aphaeresis, fractionation, and blood collection programs. One of the fundamental principles is to improve voluntary blood donation worldwide. An increase in donations will increase the overall availability of blood and blood products.

A participant from a developing country agreed that humanitarian aid is only a temporary solution. This participant emphasized the importance of governments committing to improve funding so that more factor concentrates can be purchased, products can be produced in the country, and a shift can be made to recombinant products.

Mr. O'Mahony asked whether a system under which an agreed list of countries would have access to lower-priced products for a particular period of time would be feasible.

Dr. Bult said that the answer depends on local circumstances. Cycles of supply and demand completely change market dynamics. The answer in each specific case would depend on a particular company's situation; however, in general, that route would be very problematic for manufacturers.

Mr. Skinner noted that the idea of twin-track pricing was introduced to open up discussion, just as the ideas about unused proteins were introduced several years ago. Important considerations surround this potential option in the development of sustainable care: Can issues such as re-importation be adequately addressed? Given the complex issues, this question might be best discussed in smaller forums over a longer period of time. The involvement of industry in these discussions will be key.

A participant recommended that the WFH Global Survey be expanded to include additional issues, such as prenatal diagnosis, diagnosis details, and details of gene sequencing data.

Final Discussion and Closing

Mr. Skinner offered several observations on what the Global Forum had heard, and then thanked all the speakers and participants.

The most important message, he said, is that this is a beginning—not an end. There is recognition of the tremendous unmet need for treatment. It may be possible to chart a course that will allow the global hemophilia community to move forward to improve supplies. Although some of the ideas presented were somewhat novel or controversial, many areas of convergence were also seen.

Having a comprehensive definition of risk is important, Mr. Skinner said. This definition must extend beyond the concept of safety from viruses and must include considerations of inhibitor development and lack of supply. Plasma-derived and recombinant products both clearly continue to be important. Although decisions are made on a local basis, having science to back up those decisions is also important.

Global collaboration was evidenced on several fronts. Strong international research and data are important, particularly to meet the treatment demands of patients with inhibitors and rare bleeding disorders. The WFH is willing to take a leadership role in both of these areas.

Mr. Skinner said that another clear point was that economic realities continue to be important. Despite best wishes and hopes, consciousness of economic factors is important. Improving care is the ultimate goal, but it must be recognized that it takes sustainable companies to retain their positions in the marketplace.

Hosting presentations on innovations was a first for the Global Forum, said Mr. Skinner. He clarified that the WFH was not endorsing particular projects or companies and that other companies are also doing innovative work on new or improved products. And in the discussion about humanitarian aid, it was helpful to hear about ways that such aid could be used to leverage the development of sustained care. It seems clear that post-production testing for viruses is irrelevant, and that re-validation should be examined on a country-by-country, case-by-case basis.

The Forum heard about both benefits and limits of tenders, Mr. Skinner recalled. Any good tender process starts with quality product, and price is not the only relevant determinant. The importance of having multiple companies and products in the tender process, as well as the centrality of the patient and of clinician involvement, was also clear.

Mr. Skinner concluded by describing the Forum as “a winning coalition”—a group of people who represent the various segments and interests that can actually make things happen in hemophilia treatment and care.

Appendix: Acronyms

A1PI	alpha-1 proteinase inhibitor
ATIII	anti-thrombin III
BPL	Bio Products Laboratory (United Kingdom)
CBS	Canadian Blood Services
CDC	Centers for Disease Control (U.S.)
CSL	formerly Commonwealth Serum Laboratories
CV	coefficient of variation
DDAVP	desmopressin acetate
EMA	European Medicines Agency
FDA	Food and Drug Administration (U.S.)
FFP	fresh-frozen plasma
GNP	gross national product
HIV	human immunodeficiency virus
HTCs	hemophilia treatment centres
IND	investigational new drug
IVIG	intravenous immune globulin
KGN	Next Generation Kogenate
LFB	Laboratory for Fractionation and Biotechnology (France)
MA	marketing authorization
NAT	nucleic acid amplification testing
NBI	National BioProducts Institute (South Africa)
NRAs	national regulatory authorities
PCCs	prothrombin complex concentrates
PPP	purchasing power parity
PPPS	Plasma Protein Purification System
UDC	Universal Data Collection Program
vCJD	Variant Creutzfeldt-Jakob disease
vWD	von Willebrand disease
vWF	von Willebrand factor
WFH	World Federation of Hemophilia
WHO	World Health Organization

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