WORLD FEDERATION OF
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Treatment for All

The World Federation of Hemophilia Fifth Global Forum

on the Safety and Supply of Treatment Products for Bleeding Disorders

Proceedings

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Executive summary

The Fifth WFH Global Forum on the Safety and Supply of Treatment Products for Bleeding Disorders took place in Montreal on September 24-25, 2007, and included 161 participants representing 35 different countries, 21 manufacturers, 21 patient organizations, 11 regulators from 8 different countries, and 23 hematologists and clinicians. The forum's program was designed to identify current and timely issues and respond to people with bleeding disorders' pressing questions: Am I at risk? Do inhibitors matter? What kind of product should I use? Why are products so expensive? Are there generic products available? When will there be a cure?

Opening Session

The opening session looked at quality of life (QoL) studies and recombinant and plasma product usage and cost throughout Europe. Alessandro Gringeri explained the latest research on QoL. He emphasized that health-related quality of life is measurable and that QoL assessments are effective. They indicate that hemophilia patients have poorer physical QoL than the general population, but similar scores in the psychological domains. Moreover, they confirm that patients in areas with higher factor consumption per capita report better QoL and patient satisfaction than those in other regions.

Wolfgang Schramm reported on the large range in therapeutic use of factor concentrates across Europe. He noted that the demand for both plasma-derived and recombinant products is increasing and that practice varies widely from country to country. However, guidelines should not be transferred from one country to another; it is important that they be tailored to suit individual situations. In order to ensure adequate supplies of factor concentrates for all patients, he stressed the importance of using cost-benefits analysis to guide resource allocation decisions.

Inhibitors

The session on inhibitors and recombinant versus plasma-derived products looked at one of the most pressing safety issues for people with hemophilia today. Inhibitors is a very expensive, multifactorial complication of hemophilia treatment with serious long-term consequences. The risk is greatest in previously untreated patients with severe hemophilia A, with the highest risk during the first 50 to 100 cumulative exposure days. There is great interest in the possibility that recombinant products may have a higher risk of inhibitors. The speakers in this session agreed that there is not enough data to make a determination and that more studies are required. Mike Soucie reported on progress that is being made in developing such studies.

Jenny Goudemond discussed evidence that suggests there is a link between use of recombinant products and inhibitor development, calling for better understanding of the underlying mechanisms that account for this in order to bioengineer novel, less immunogenic molecules. Marijke van den Berg reviewed evidence that suggests that recombinants are not more strongly associated with inhibitor development. She noted that the intensity of the first exposure to clotting factor concentrate (CFC) and the use of prophylaxis do seem to be two factors that do make a difference and can be controlled. Wolfhart Kreuz reviewed the evidence on the association of von Willebrand factor (VWF) and inhibitors. He called for more studies but argued that the role of VWF may significant.

Keith Hoots concluded the session by saying that as a clinician, he felt it is premature to change prescribing practices. He noted that in the patient community concern about perceived risk and a cautionary approach are very strong. The necessary data to compare pathogen risk and inhibitor risk properly has not yet been gathered.

Economics of treatment

The session on the economics of the global market in treatment products for bleeding disorders looked at the high cost of treatments for bleeding disorders, the future of the world supply and the technical, political, and economic decision-making that shape the market. Paul Walton described how new products for rare disorders can get to market. Jeff Stonebraker discussed the complexities of the oligopolistic global factor VIII (FVIII) market and how it may continue to mature. Ms. Jane Martin explained the challenges of manufacturing in an industry with high fixed costs, a slow production cycle, and unpredictable and fast-moving demand. Albert Farrugia discussed the role that political decision making has in the cost of products, concluding that the concern of policy makers with the cost of health care and the continuous expansion of healthcare costs, including for people with hemophilia, will be scrutinized by policy makers in the foreseeable future and the hemophilia community should be vigilant and concerned.

Generic biologics and biosimilars

Generic medicinal products can make great savings in other healthcare sectors and the session titled "Biosimilars: Regulatory issues" looked into the possibility that biosimilars could make a difference in the bleeding disorders community. Because of immunogenicity, all four regulators who spoke agreed that licensing of biosimilar products will not be nearly as easy as for chemical products. It is difficult to prove that two biological products are exactly the same, in particular with a large molecule like FVIII. However, governments are developing regulatory pathways to allow this to happen. Sol Ruiz discussed some of the technical challenges in comparing biologics and described the European process which has already licensed one biosimilar product.

Mark Weinstein spoke about the US "follow-on biologics" process and described some of the differences between biologics that are of great concern as regards immunogenicity. Anthony Ridgway talked about some of the ways that comparing products can be streamlined, noting that complex products cannot be compared the way simple chemical medicines can. Dr. Farrugia agreed with his regulatory colleagues on the challenges of approving "generic biologics" but suggested other ways that developing countries might approach the issue, including technology transfers.

National tenders

National tenders are becoming increasingly popular as a way to acquire treatment products for bleeding disorders. These are being used in countries with very different economies and varied objectives. Sorakij Bhakeecheep said the tender process in Thailand had the goal of increasing the supply of CFCs at an affordable price. In Thailand the price per IU was negotiated down from US$0.40 to US$0.20 but has since crept back up slightly. Sylvia Thomas said that the Brazilian tender process was intended to fulfill the constitutional right to free adequate care for all people with hemophilia. Unfortunately Brazil still faces occasional shortages and uncertainty in supply. She called for a rethinking of the Brazilian system. Paula Bolton-Maggs said that the UK tendering system, by heavily involving clinicians from the outset and by using advanced data systems and careful analysis has managed to save the UK money while maintaining high levels of care. Sophie Ludgate said that a manufacturer can support tenders that are transparent and fair and include clinicians and patients in the decision-making process. She noted the potential risks of national tenders, in particular limitations on clinical freedom and the opportunity to increase prophylaxis or access to new therapies and treatment caps.

Longer-acting factor concentrates

The innovation in hemophilia treatment which is perhaps closest to being available on the market is longer-acting factor concentrates. Two of these products were described by Glenn Pierce and Bruce Ewenstein. The products use PEGylated liposomes to prolong the half-life of FVIII. It is hoped that products with a longer half-life will mean a reduction in infusion frequency for people with hemophilia. Furthermore, if it is possible to keep trough levels permanently above 1 per cent, this should significantly reduce hemarthroses. Yuri Zhulyov, who participated in a trial for one of the products, said that he looks forward to the development of new products that will reduce the number and frequency of injections and also sees other advantages for patients in large countries like his native Russia.

Gene therapy

Hemophilia is a well-understood genetic disorder and has been a candidate for treatment with gene therapy since the early 1980s. Glenn Pierce reviewed the history of gene therapy, calling it a story of "two steps forward, one step back." He noted that hemophilia has effectively been cured in mice and dogs but taking that technology to humans has met with challenges that have yet to be resolved. Dr. Pierce concluded that although progress is being made and a cure is foreseeable, it is important not to forget that most people with hemophilia are untreated and that if they don't get access to existing replacement therapies, they will never be able to benefit from gene therapy. David Lillicrap discussed the future of gene therapy for hemophilia. He described in detail some of the current issues affecting gene therapy and noted that we will probably not see results within the next five years. Continuing challenges include host immune response to both the vector and transgene product, achieving persistent therapeutic levels of transgene expression, and insertional mutagenesis.

Safety and supply issues

Two speakers addressed emerging and ongoing safety and supply issues. Dr. Farrugia discussed the variant Creutzfeldt-Jakob disease (VCJD) risk assessments that came out early in 2007 as well as new technologies to deal with prions. He said the most interesting emergent agent in the past year or two has been pandemic influenza. He reviewed several studies that suggest how to deal with blood supply in face of a pandemic. Fractionation and inactivation models developed for influenza indicate that this virus is inactivated by processes that already exist, such as vapour heating, solvent detergents, and pasteurization in albumen.

At this time, recipients of factor concentrates can be relatively at ease about the safety of products, Dr. Farrugia concluded. Bruce Ritchie spoke about post-marketing surveillance, emphasizing that it is essential to monitor as many patients as possible and that for small patient populations this means international collaboration is important. He added that surveillance must be conducted in a more organized, systematic fashion and must examine all kinds of rare adverse events—not just pathogens and inhibitors. As gene therapy and transgenic treatments come on-line, it will be challenging to design rigorous studies and appropriate surveillance.

Innovations

The Global Forum concluded with a session on innovations in treatment products. Dr. Bolton-Maggs gave an overview of the treatments available for the very rare disorders. The WFH has seen increasing numbers of patients with these disorders identified but choice of treatment products is still quite limited. While treatments do exist for factor VII (FVII), factor XI (FXI), and factor XIII (FXIII) deficiencies, no treatments are available for prothrombin, factor V (FV), and factor X (FX) deficiencies. Dr. Bolton-Maggs noted that

several companies are working on developing new, safe treatments for these extremely rare disorders. Magdi El Ekiaby presented an overview of a program to prepare viral inactivated, solvent-detergent-treated cryoprecipitate, cryo-poor plasma, and plasma for use by blood establishments. The products can be used to treat hemophilia A and B, von Willebrand disease (VWD), fibrinogen deficiencies, and severe postpartum bleeds. Future innovations may allow for mini-pool preparations of prothrombin complex concentrate (PCC), factor IX (FIX), FVII, FXI, and FV. Yann Echelard and Sam Chtourou described a project to provide an abundant, cost-effective, safe source of factor VIIa (FVIIa) for human therapeutic use by producing recombinant human coagulation FVIIa (rhFVIIa) in the milk of transgenic animals. Ed Gomperts discussed the development of a new recombinant factor IX (rFIX) in an attempt to make treatment more economical, treat more patients, and allow more patients access to prophylactic care.

Welcome

World Federation of Hemophilia (WFH) president Mark Skinner welcomed participants to the Fifth WFH Global Forum on the Safety and Supply of Treatment Products for Bleeding Disorders. Noting the broad range of perspectives represented at the meeting, he identified attendees representing 35 different countries, 21 manufacturers, 21 patient organizations, 11 regulators from 8 different countries, and 23 hematologists and clinicians.

The Forum's program is designed to identify current and timely issues, Mr. Skinner said. People with bleeding disorders continue to have pressing questions:

- Am I at risk?
- Do inhibitors matter?
- What kind of product do I use?
- Why are products so expensive?
- Are there generic products available?
- When will there be a cure?

He expressed hope that discussions at the Global Forum would illuminate some of these questions. "We don't expect absolute answers, but we do hope to move further along in our understanding, and to get a sense of what the audience is thinking and how that evolves over time." The meeting is intentionally kept small to allow many opportunities for feedback and discussion, so he encouraged participants to challenge and engage the speakers.

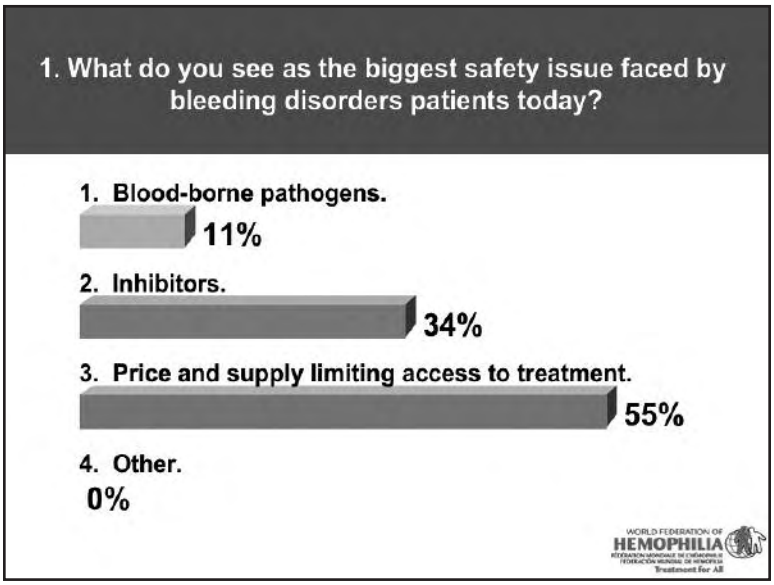
Acting chief executive officer of the WFH Claudia Black thanked the participants for their warm reception and extended her welcome and thanks to all in attendance. She also thanked the sponsors of the Global Forum: André de la Porte Foundation; Héma-Québec; Ministère des rélations internationales, Gouvernement du Québec; Ministère de la santé et des services sociaux, Gouvernement du Québec; and the Public Health Agency of Canada.

David Page, president of the Canadian Hemophilia Society and chair of the WFH Safety and Supply Committee added his welcome to participants. He also explained that hand-held voting machines would be used to poll participants on a number of questions throughout the Forum, in order to assess the attitudes and concerns of the bleeding disorders community regarding key issues, as well as to track changes in perception that might arise as a result of presentations over the course of the days' discussions.

Question 1

What do you see as the biggest safety issue faced by bleeding disorders patients today?

Blood-borne pathogens	11%
Inhibitors	34%
Price and supply limiting access to treatment	55%
Other	0%



Powerpoint slide from WFH Fifth Global Forum on the safety and supply of treatment products for bleeding disorders

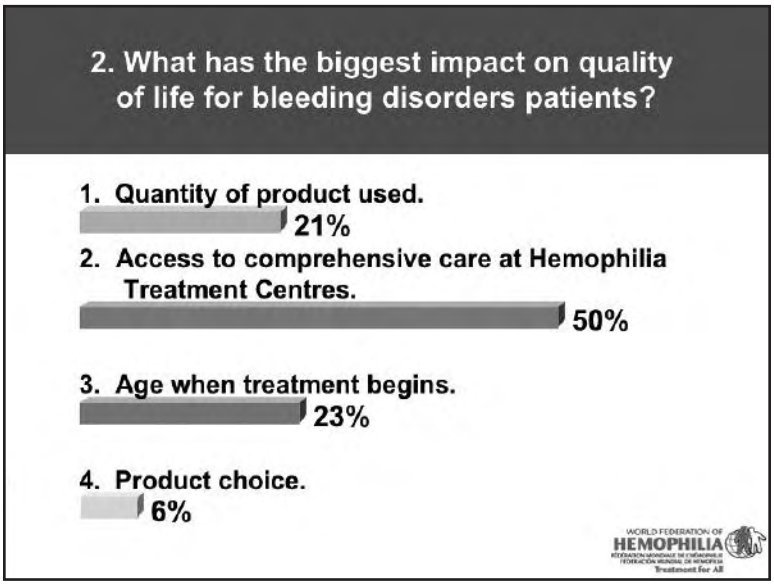
Opening session

Paul Giangrande, WFH vice-president medical and chair of the opening session described the forum's program as very exciting from a clinician's perspective. Prior to introducing the session's speakers, he polled the audience.

Question 2

What has the biggest impact on quality of life for bleeding disorders patients?

Quantity of product used	21%
Access to comprehensive care at hemophilia treatment centres	50%
Age when treatment begins	23%
Product choice	6%



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Quality of life studies: Delivery of care issues

Alessandro Gringeri, A. Bianchi Bonomi Hemophilia and Thrombosis Centre, University of Milan, Italy

Alessandro Gringeri began by explaining what quality of life (QoL) is and why it's important. In essence, QoL is the patients' own perception of their well-being or health. Many clinicians are reluctant to accept patients' opinions but it is important to know how they rate their health and the outcome of the care that is being provided. While he conceded that QoL is subjective, it is also very real and there are validated, standardized instruments to quantify it. They allow comparison between different health conditions and are sensitive enough to capture differences over a period of time.

Dr. Gringeri presented the results of a European Haemo-QoL study, conducted by V. Mackensen and S and M Bullinger that compared outcomes for children in six western European countries using the KINDL scale. The study found that the perception of well-being in patients with hemophilia was roughly similar to other patients with minor health conditions, such as asthma or obesity. He cautioned that children with hemophilia scored somewhat lower in the school and self-esteem dimensions, which warrants consideration.

The same study revealed significant differences from country to country in the total QoL scores for children living with hemophilia. Even though all the countries involved in the study were Western European countries with high availability of concentrates, the scores indicated that QoL is perceived as substantially better in Germany and the Netherlands than it is in France and the UK. Understanding the reasons for this is important so that there can be appropriate responses, he said.

Italian studies of QoL in adults (based on the European Health Economic Study: SF-36 domains) scored physical functioning, physical role, pain, general health, vitality, social functioning, emotional roles, and mental health and allowed comparison between the adult male population in general and people with hemophilia from the Cost Of Care Inhibitors Study (COCIS) and the Cost Of Care of Hemophilia Study (COCHE). Findings suggested a significant difference in assessments of physical functioning, but scores for vitality and mental health were similar.

A Western European study published by the European Hemophilia Economic Study Group demonstrated that people with hemophilia scored below the normative population in most of the physical domains but, again, scored more closely in the emotional and mental domains. That study also indicated that patients receiving prophylaxis scored significantly better than those receiving on-demand treatment, particularly in the physical domains.

The European Study of Clinical, Health economic and Quality of Life outcomes in Haemophilia treatment (ESCHQoL), coordinated by Wolfgang Schramm, compared QoL of patients in 21 countries divided into three subsets: those with more than 5 IU factor per capita; those with between 2 and 5 IU per capita; and those with less than 2 IU per capita. For every domain, except family, there was a significant difference in QoL scores depending on the availability of treatment. In children, overall quality of life scores were substantially better in every age group for those with access to higher amounts of treatment products.

Dr. Gringeri concluded by stressing that health-related quality of life is measurable and that QoL assessments are effective. They indicate that hemophilia patients have poorer physical QoL than the general population, but similar scores in the psychological domains. Moreover, they confirm that patients in areas with higher factor consumption per capita report better QoL and patient satisfaction than those in other regions.

Recombinant and plasma product usage and cost throughout Europe

Wolfgang Schramm, Department of Haemostasis and Transfusion Medicine, University of Munich, Germany

Using data he had collected over the past 10 to 15 years, Wolfgang Schramm reviewed issues relating to recombinant use and cost throughout Europe. Dr. Schramm reminded participants of the 1999 Wildbad Kreuth Initiative, which recommended that adequate coagulation factor concentrates should be available throughout Europe and that quantities of both plasma-derived (PD) and recombinant treatment products should be maintained, while acknowledging that recombinant products would likely gradually supplant those that were plasma-derived.

Dr. Schramm noted that factor replacement usage varies widely both within the European Union and between the EU and other European nations. Data on FVIII use from 2004–2005 shows a wide disparity with most countries in the 3 to 4 IU per capita range. Sweden and Germany had the highest usage levels at 6.5 and 5.5 IU per capita respectively, while Bulgaria, the Baltic States, Russia, and Romania had the lowest with usage rates below 0.5 IU per capita.

There is a wide range of factors influencing this supply, he said. They include completely different styles of healthcare systems, medical guidelines that vary widely from country to country, financial conditions, and the availability of clotting factor concentrates.

The price structure also varies from country to country with different levels of wholesale and retail mark-up and taxes. As a result, Dr. Schramm observed that prices fluctuate by plus or minus 20 per cent, even within the EU. Average selling prices for plasma-derived products vary from lows of US$0.12 per unit in Poland (with other Easter European countries including the Baltic States, Russia, and the former Yugoslavia all seeing average prices below US$0.20 per unit) to US$1.11 in Denmark. Recombinant prices range between US$0.55 and US$1.02.

The ratio of plasma-derived versus recombinant products also varies widely. Data presented from 2005 indicates that Eastern European countries depend entirely on plasma-derived products, while EU member states not only tend to have higher usage rates per patient, but higher proportions of recombinant products. France used nearly 90 per cent recombinant products; Denmark, 86 per cent; and the UK, 85 per cent. Recombinant use levels in Germany were around 45 per cent.

Those countries with the highest per capita Gross Domestic Product (GDP) use the highest levels of factor, Dr. Schramm said, while those with the lowest per capita GDP tend to have the lowest usage levels. However, wealth does not always directly correlate with factor usage levels. The Czech Republic, Hungary, and Slovakia—all with per capita GDP below €10,000 are in the middle range for factor usage. Greece, on the other hand, with per capita GDP of €16,455 uses only 1.5 IU per capita.

Again, there are broad ranges in product usage revealed by the European Social Economic Study ESCHQoL. Three countries—Germany, Italy, and Spain—use twice the amount of FVIII as 19 other European countries combined. Similarly, Germany, the UK, France, and Italy use four times as much recombinant product as 13 other European nations combined.

Dr. Schramm concluded by reiterating the range in therapeutic use of factor concentrates across Europe. He noted that the demand for both plasma-derived and recombinant products is increasing and that practice varies widely. However, guidelines can't be transferred from one country to another; it is important that they be tailored to suit the individual situation. In order to ensure adequate supplies of factor concentrates for all patients, he stressed the importance of using cost-benefits analysis to guide resource allocation decisions.

Discussion

David Page said that he was surprised that the data suggested that QoL was similar for patients with and without inhibitors.

Alessandro Gringeri mirrored that surprise. He explained that while results were similar, they were not equal. The greatest similarities were in the social dimensions, while differences were somewhat more marked in terms of the physical domains. Findings like these underscore the importance of asking patients questions about their own treatment, he said.

Wolfgang Schramm said his studies also indicated the same patterns in QoL scores for patients with inhibitors versus those without.

Recombinant versus plasma-derived: inhibitors

Chair Paul Giangrande opened the session by polling the audience, noting that he would repeat the same question after the session's presentations had concluded.

Question 3

Do you believe that recombinant clotting factor concentrates carry a higher risk of inhibitors than plasma-derived products?

Yes	28%
No	17%
Possibly, but need more data	40%
Unlikely, but need more data	15%

Update on global collaboration in studies on inhibitors in hemophilia

Mike Soucie, Associate Director for Science, Division of Blood Disorders, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA

- Mike Soucie related a number of important events that had occurred since the ast Global Forum and updated attendees on recent progress in promoting global collaboration. Some of the key events that have taken place since 2005 include the following:
- An expert meeting hosted by the Blood Products Working Party of the European Agency for the Evaluation of Medicinal Products (EMEA) in February 2006, whose report included recommendations for guidance on clinical investigations of recombinant and plasma-derived FVIII products
- A meeting of the International Society on Thrombosis and Haemostasis (ISTH) FVIII and FIX Sub-committee in 2006 that compared US and UK data systems and made recommendations for harmonization and sharing of data collection instruments

The presentation of a plan for harmonized data collection on inhibitors by the UK and Germany at the 2007 ISTH FVIII and FIX Sub-committee meeting

In describing the US Pilot Study of Post-Market Surveillance for Inhibitors, he explained that providing data coordinator support to get factor exposure data and to ensure annual testing was an important study component. The study design is a prospective cohort of patients of all ages with hemophilia A or B. Subjects will be tested for inhibitors annually and prior to any product switch. Complete genetic sequencing will be done at the CDC laboratories.

So far, nine centres have enrolled 526 patients representing a wide range of ages, racial characteristics, historical exposure days, and positive inhibitor histories. Four of the pilot sites will also enrol babies, Dr. Soucie said. Data collected will include infusion logs, dose, reason for infusion, and product brand. In addition, patient adherence rates will be collected at each centre. It is expected that patients' infusion logs will improve over time.

To date, 538 inhibitor titre measurements have been done on patients with hemophilia A, and 121 on hemophilia B patients. More than 500 patients have received genetic testing; 240 of those tests are completed and 153 have already been reported. Seventy patients have already submitted more than one sample.

Of 435 patients with no history of inhibitor who have been tested, slightly more than half registered zero Nijmegen-Bethesda Units. Forty-eight per cent registered between 0.1 and 0.4 units and 6 patients (1.4 per cent) had test results greater than 0.4 Nijmegen-Bethesda Units.

Dr. Soucie said that the study had already resolved some questions regarding inhibitor data collection, namely that there is no specimen degradation if shipped by cold-pack and that residual FVIII in specimens can be removed by heating prior to testing. Research is underway to determine whether chromogenic assays are more reproducible than clot-based assays. However, important questions remain unresolved. He invited participants to provide feedback on what the cut-off should be for a positive test and what the clinical implications of low-titre inhibitors might be.

The genetic testing being conducted includes sequencing of the full gene forward and reverse with the promoter and the validation of all mutations identified in gene sequencing. Reporting identifies the precise location of the hemophilia gene defect and all mutations are checked against the HAMSTERS international data base. In addition, he said, results of the genetic tests are reported to the patients' physicians.

There are many benefits to this type of study, Dr. Soucie noted. Large population monitoring provides enough power to study rare events. International collaboration will not only increase the study power but will also increase the diversity of the products being monitored. Post-market surveillance permits patients and clinicians broad product choice and avoids random assignment. In addition, he said, quality control is facilitated through centralized testing facilities, while standardized protocols strengthen the overall validity and usefulness of the study.

Dr. Soucie concluded by acknowledging the members of the study working group and pointing out that the funding for the project is provided through a public-private partnership between Wyeth and the CDC Foundation.

The link between recombinants and inhibitor risk

Jenny Goudemand, Institut d'Hématologie, Hôpital Cardiologique, Lille, France

Jenny Goudemand prefaced her remarks by observing that there seems to be general agreement that inhibitor development is the most severe complication of hemophilia treatment today and the most frequent. The risk is greatest in previously untreated patients (PUPs) with severe hemophilia A (up to 30 per cent), with the highest risk during the first 50 to 100 cumulative exposure days (CEDs).

She reminded participants of the Wight Paisley review, which found the cumulative risk of inhibitors increased three-fold from 0 to 12 per cent in patients treated with a single plasma-derived factor VIII (pdFVIII) to 36 to 38 per cent in those treated with recombinant factor VIII (rFVIII). It was not clear, however, whether this proportion reflected the natural incidence of inhibitors in a carefully selected and monitored population compared with small and not prospective studies of patients treated with pdFVIII. In addition, most of these studies did not take other genetic and non-genetic inhibitor risk co-factors into consideration.

Dr. Goudemand reviewed the cohorts in three separate studies: the French Cohort, the CANAL study, and the UK Cohort. On reviewing the methodologies of each study, she noted that the CANAL and UK Cohort studies contain patients who have been treated for at least 50 CEDs, while the French Cohort does not. The UK Cohort study lacks a survival analysis.

Even though there are differences in some of the study results, the relative risk of inhibitors is more or less common to all three studies, she said. A multivariate analysis of inhibitor risk demonstrates that there is a common trend in all three cohorts (with marginal overlapping) to an increased risk of inhibitor in patients treated with rFVIII. The inhibitor risk is highest during the first 50 CEDs, particularly in the first 10 to 20 exposure days. First exposures are most important, Dr. Goudemand said, stressing that there is a difference between PUPs and MTPs (minimally treated patients).

There are two analysis options regarding the product effect, she said. The first is to consider risk independently of when the product is received. The second is to assume that the risk is mainly determined by the product received at the first injection (that is, that the product is a fixed covariate and data are censured after the first switch).

The authors of the CANAL study analyze their data after the first switch, Dr. Goudemand noted. If data from after the first switch is censured, however, the adjusted relative risk (aRR) of rFVIII compared to pdFVIII containing high von Willebrand factor (VWF) increases from 1.2 to 1.5. This analysis option could explain part of the difference between results of the CANAL study and French Cohort studies.

Dr. Goudemand asked participants to consider what needed to be done to demonstrate conclusively whether or not there is a difference in inhibitor risk between patients using plasma-derived or recombinant products. Several other clinical studies are already underway, including the SIPPET randomized clinical trial and several prospective cohorts. Cohorts containing 200 to 500 PUPs would be large enough to demonstrate an aRR of about 2, if the patients can be followed until at least 50 CEDs, she said. Experimental animal or in vitro research would also be helpful.

Several different hypotheses could explain the difference in inhibitor development risk, she noted. These include the presence of VWF and its protection of FVIII, the effects of the presence of TGF ,1 and other cytokines, FVIII haplotypes, protein misfolding, the difference in FVIII glycosylation, and the difference in FVIII affinity to phospholipids. Very few studies have been done to try to understand what might cause the apparent differences in risk, Dr. Goudemand said.

In concluding, Dr. Goudemand conceded that there is no certainty about higher inhibitor risk being associated with recombinant products, but there is a convergence of the results of several European studies that warrants follow-up. The real possibility of this increased risk must be taken into account by the medical, scientific, and pharmaceutical communities. It is critically important, she stressed, to understand the underlying mechanisms that account for the differences and to use that understanding to help bioengineer novel, less immunogenic molecules. Because clinical studies will take a long time to complete, it is imperative to reinforce them with experimental research, not just because of the economic implications in developed countries but also because of the potential catastrophe that could await the huge populations of patients receiving little or no treatment in developing countries.

Influence of treatment strategies on inhibitor development

H. Marijke van den Berg, Director, Van Creveldklineik, Netherlands

Marijke van den Berg began by presenting case study information on a set of monozygotic twins with severe hemophilia A and an inversion. The twins share the same gene defect, were treated with the same clotting factor product, and had the same history of vaccinations. However, Twin A developed an intracranial bleed at 7 months of age, which required therapy. After 14 days, he developed a high-titre inhibitor. Following that, he received immune tolerance induction (ITI) for 16 months, during which he developed multiple infections and several significant bleeds, and had two different central venous access devices installed.

Interestingly, his twin had only minor bleeds and developed a low-titre inhibitor, which was treated with ITI for a short period around the age of 15 months, followed by prophylactic treatment. Dr. van den Berg noted that the significant differences between the two were the age at first treatment, the intensiveness of treatment, the severity of bleeds, and the development of low versus high-titre inhibitors.

Next, she presented an overview of the CANAL study, a large retrospective cohort study involving 366 patients at thirteen European and one Canadian centre. Its goal is to study treatment-related risk factors in severe hemophilia. The study has complete data on 320 patients, 24 per cent of whom have inhibitors. Of those, 79 per cent had high-titre inhibitors and 21 per cent low titre at 50 CEDs.

By examining outcomes at peak treatment moments, it was concluded that patients treated intensively in their first exposure to FVIII had a 3.3 increased relative risk of developing an inhibitor. It also revealed that early prophylaxis provided 60 per cent protection against inhibitor development. These findings are important, she said, because gene defects and other factors that influence inhibitor development cannot be changed, but treatment regimens can be adjusted to improve outcomes.

The aim of the CANAL II study was to investigate whether plasma-derived products induce fewer inhibitors than recombinants, whether plasma-derived products with higher VWF have lower inhibitor incidence, and whether product switching has an impact. Dr. van den Berg explained that products were divided into three categories, according to their VWF:Ag content:

- Those containing no VWF:Ag (recombinant products)
- Those with little VWF:Ag (monoclonally purified pdFVIII)
- Those with high amounts of VWF:Ag (all other pdFVIII products)

A total of 316 patients were included in the study and data were adjusted for ethnicity, gene mutation, age at first exposure, duration between exposure days, baseline FVIII:C, dose of FVIII, and prophylaxis. The data indicate similar inhibitor development with recombinant and plasma-derived products, after adjustment for other confounders. In addition, there was no apparent increased risk after product switching. Finally, Dr. van den Berg noted, high-purity, low-VWF-containing products appear to lower inhibitor incidence. However, she cautioned that the patient group studied was too small to draw clear conclusions.

Von Willebrand factor and inhibitors

Wolfhart Kreuz, Department of Pediatrics, Johann Wolfgang Goethe–University Frankfurt am Main, Germany

Noting that inhibitor development is the most severe complication in previously untreated patients (PUPs) and that inhibitor elimination can be extremely difficult, Wolfhart Kreuz said it is necessary to understand the multiple genetic and exogenous variables that play a role. Determining whether the type of concentrate used or its VWF content play a role in inhibitor development is extremely important.

Presenting the cumulative data from several single recombinant and plasma-derived studies, he highlighted findings from PUP studies in the UK where 27 per cent of those treated with rFVIII developed inhibitors, in comparison with only 14 per cent of those treated with pdFVIII. In the CANAL Study of clinically relevant inhibitors, 29 per cent of patients treated with rFVIII developed inhibitors, as did 24 per cent of those who received pdFVIII containing more than .001 IU of VWF per IU of FVIII:Ag. However, only 15 per cent of those treated with low-VWF pdFVIII developed inhibitors.

The problem, Dr. Kreuz said, is that it is impossible to compare most studies because of different design, study populations, and methodologies. Both comparative and randomized studies are needed. Studies must be prospective, use central laboratories, and take sufficient inhibitor measurements. The most crucial time to measure inhibitors is at the time of first exposure (between 0 and 20 CEDs), so early childhood is the time to enrol patients in the studies.

Dr. Kreuz said the only prospective study conducted to date is the German, Austrian, and the Swiss Society of Thrombosis and Hemostasis Research (GTH) study, a prospective study examining inhibitor induction in PUPs with hemophilia A and B. Although it is still too early to reach firm conclusions, the trend seems to indicate an increased likelihood of inhibitor development with rFVIII.

Several hypothetical considerations could explain the differences in inhibitor development:

- Manufacturing process (e.g., recombinant technologies, different purification, and virus inactivation methods)
- Impurity of pdFVIII products with other immunomodulatory peptides (e.g., TNF-alpha)
- Presence of VWF

There are several theories that may explain the apparent impact of VWF on inhibitor development, Dr. Kreuz said. These include the possibility that VWF protects FVIII against degradation by proteinases, and that VWF protects FVIII from endocytosization by human dentritic cells, which may reduce immunogenicity.

Studies on the relationships between FVIII:Ag and FVIII in plasma-derived and recombinant concentrates may also yield an explanation, he said. Recombinant products contain 25 per cent more FVIII:Ag than plasma-derived concentrates. Twenty per cent of the rFVIII:Ag was not able to bind exogenous VWF. The biologic consequences of the FVIII:Ag that is not able to bind to VWF is not known. However, this difference may be related to the different rates of inhibitor development.

Mouse studies have found significantly higher inhibitor titres in mice treated with both plasma-derived and recombinant products depleted of VWF, and other studies suggest that immunomodulatory peptides in pdFVIII may have an impact on inhibitor formation, Dr. Kreuz said. While all these results are interesting, they point to the need for more prospective studies, randomized trials, and case-controlled studies.

More study is also needed regarding immune tolerance induction therapies, he said. In vitro observations suggest that there is lower inhibitory activity against FVIII with VWF than rFVIII in inhibitor plasmas with anti-C2 specificity, and that increased amounts of VWF in FVIII concentrates has a protective effect. In vivo study found higher recovery rates when infused FVIII contained VWF in hemophilia A patients with an anti-light chain FVIII inhibitor.

Dr. Kreuz also presented study results from a number of other centres that suggested a correlation between the success of ITI and the presence of VWF in concentrates used. However, study populations were small and study methodologies varied. Again he stressed the need for prospective randomized ITI studies, such as the RESIST study and the Observational ITI Research Program, to ensure that patients are truly comparable.

A physician perspective on choice of product type on the risk for inhibitor development/likelihood for successful ITI

Keith Hoots, Director, Gulf States Hemophilia and Thrombosis Center, Department of Pediatrics, University of Texas Houston Health Sciences Center, Texas, USA

Keith Hoots began by re-emphasizing several points "elegantly" made by other presenters from a clinician's point of view: that there is a lack of randomized study data; that there are challenges presented by covariant confounding effects; that most prospective PUP studies consist of small numbers with short follow-up periods. Overall, true incidence data, adequately stratified for risk factors is scarce, which makes non-prospective, non-concurrent comparisons problematic.

The primary question, Dr. Hoots said, is whether or not plasma-derived FVIII products confer less risk for de novo high-responding inhibitors. These are the patients that see the greatest impact on the physical scale, so it is with these patients that the key to answering the question lies.

"How much would the risk of an inhibitor have to be reduced to influence the choice of a plasma-derived versus a recombinant product for a previously untreated patient?" he asked. As a follow-up, he posed another question: If a rVWF product were available, and if it were clear that the presence of VWF accounted for most of the decreased risk, would a combined rFVIII/rVWF therapy be a preferred choice for PUPs?

He reminded participants that polling at the Forum indicated that inhibitors have overtaken product safety as the biggest issue of concern in the bleeding disorders community. Still, 13 per cent of those polled cited safety as their leading concern. As a community, a perceived risk and cautionary approach has been inculcated into patients. With it comes a mindset that higher purity is better. The question being asked now is whether that is true and how much of a higher risk for inhibitor development would counterbalance those safety concerns.

It is clear that more than genetic/ intrinsic host risk factors are at play where inhibitor development is concerned, Dr. Hoots said. External and environmental risk factors also play a role. So, studies must be designed to control for covariate risk and account for possible confounders when trying to determine causality for inhibitor development, which can be extremely difficult when relatively infrequent events occur in small populations.

Because of the design limitations of the studies to date, Dr. Hoots said it is premature to change prescribing practices. He cited several reasons:

- Although selected pdFVIII use outcomes regarding inhibitors have been reported retrospectively, powered prospective randomized studies have not been done
- Large retrospective studies indicating increased inhibitor risk with rFVIII were not controlled for relevant confounders
- The overall population inhibitor risk has not changed significantly over the past two decades with the introduction of recombinant products
- Even if there is a reduced risk with pdFVIII, it is not clear that VWF is the reason
- Even doubly viral-inactivated pdFVIII appears to be immune suppressive, which may not be desirable

There are also other important considerations, Dr. Hoots said. Early prophylaxis might make this discussion moot, since it appears that rFVIII prophylaxis in PUPs may compensate for the reduced risk associated with plasma-derived factor. In addition, gene transfer is a very real possibility for hemophilia in the near future. It will be done with rFVIII or rFIX and the immunogenicity issues may require novel solutions.

Supply also continues to be an important issue, Dr. Hoots noted. An adequate global supply is dependant on the presence of both plasma-derived and recombinant products, so clinical decisions cannot be made within narrow contexts. Finally, while all current products are pathogen safe, it is unlikely that safety considerations will ever disappear completely and the reality is that rFVIII has the highest theoretical safety profile.

Discussion

Chair Paul Giangrande repolled participants and noted there had been a significant shift in people's views about possible risks.

Question 3 (repeated)

Do you believe that recombinant clotting factor concentrates carry a higher risk of inhibitors than plasma-derived products?

Yes	28% (28% first time)
No	10% (17% first time)
Possibly, but need more data	52% (40% first time)
Unlikely, but need more data	12% (15% first time)

Albert Farrugia commented that, while clinical data is increasingly compelling, putative explanations are not. If 20 per cent of FVIII antigen does not associate with VWF, this should be reflected in the pharmacokinetics, but it is not.

Dr. Kreuz responded that all recombinant products lack VWF. In the 14-year study of PUPs at his centre on children treated prospectively using a central lab, there has been a big difference between plasma-derived and recombinant products. That difference warrants discussion.

Alessandro Gringeri said that randomized trials in PUPs will commence soon, noting they will be partially financed by industry. He asked Keith Hoots if he would change recommendations for those at high risk of inhibitor development if these studies demonstrate a 50 per cent reduction in risk for inhibitor development with the use of pdFVIII.

Dr. Hoots replied that the solution is a better biologic understanding of patients. If there is no demonstrable underlying risk and, assuming a 50 per cent total risk, he said he would not likely change his recommendation if the risk was reduced to .3 or higher.

In response to questions about the appropriateness of starting prophylaxis early to avoid inhibitor development, Dr. van den Berg said that her group was working on developing a good risk model to help determine which patients have the highest risk. Dr. Kreuz said that the first six months of life are the time when inhibitor risk is highest, so he recommended against starting prophylaxis during that time.

The economics of the global market in treatment products for bleeding disorders

Chair Mark Skinner introduced the session on the economics of the global market in treatment products for bleeding disorders by twice presenting a question for voting, once to the general audience and then only to representatives from pharmaceutical companies.

Question 4

What do you believe is the most important economic factor impacting product pricing?

R&D costs	30%
Production costs	15%
Competition	20%
Economy of the country where it is being produced:	34%

Question 5

What do you, as a participant representing a pharmaceutical company, believe is the most important economic factor impacting product pricing?

R&D costs	43%
Production costs	24%
Competition	15%
Economy of the country where it is being produced:	19%

Economic factors impacting the development of new biotherapies for rare diseases

Paul Walton, Senior Vice President, Business Development, CSL Behring

Paul Walton explained that his presentation originated a few years ago from a workshop on the economics of rare diseases and would explore the decision-making factors that companies employ when determining whether to invest in new products. "None of this is economic rocket science," he said. Any company—whether it manufactures biomedical products or pipes—has to make the same decisions on timing, research and development, and competitiveness issues.

Hemophilia falls into the category of rare diseases. There are 7,000 rare diseases that affect about 25 million people in the United States, which on a worldwide basis means that there are 500 million people affected globally. The legal definition of a rare disease under the "orphan disease" category varies according to the country. Canada and many other countries have no official "orphan disease" designation.

This is an important category for pharmaceutical companies to consider. Although the cohort of patients is small relative to the population, there are some incentives and reasons for developing drugs, including exclusivity and an unmet medical need. Next, some current therapies could have limitations such as cost, supplier capacity, or global reach, or be no longer available because of regulatory or safety issues. Sometimes there are also life-cycle improvements or companies could see a commercially attractive opportunity, such as the end of a patent or orphan drug status.

Internally, companies involve Leadership, Strategy, Business Processes, and Planning in their decision-making processes. External factors that influence decisions include raw materials and supplies, markets, and customers. For biotherapies, the customers are actually the company's customers' customers—the patients. Many factors have to be considered, including government regulations and policies, economic conditions in the marketplace, patient and community concerns, technology, shareholders, competitors, and the parent company. The complexity of this decision-making process shows that qualitative issues as well as economic ones determine the eventual outcome.

Dr. Walton noted that there are guiding principles for determining when to develop new products or therapies. A company is responsible to both the patients and its shareholders who provide the capital.

Developing biotherapies involves significant capital investments and comes with a significant risk of failure. In fact, said Dr. Walton, most new biotherapies fail in their pivotal clinical trials for safety and efficacy. The biotechnology industry has yet to break even. This risk of failure has to be taken into account when modelling for investment in new therapies.

Companies typically use investment analysis techniques that simulate the development of a new product when faced with complex projects that involve significant capital and investment and long timelines prior to launch. Dr. Walton said that CSL Behring focuses on net present value, cash flows, qualitative factors, and possible investment alternatives before deciding whether to proceed. The process never really ends, said Dr. Walton—some projects "on the shelf" are revisited when conditions change. Even when a decision is made to go ahead with a project, the assumptions and decisions are always rechecked.

Safety, efficacy, and the potential impact on patient welfare are the major factors that influence the decision rules for investment in new therapies. If a drug fails in trials, the impact on the shareholders and share price is immediate; a number of companies have not survived this step. Companies also look at the capital investment required to manufacture the product; the number of potential users; orphan drug designation; in-market issues such as anticipated reimbursement, product pricing, and competition; and the cost of manufacturing at the required scale. In addition, they look at the cost of chemistry, manufacturing, and controls; the cost of clinical trials; royalty costs (which can be as high as one-quarter the costs of the entire project); the time it takes to launch and then reach peak distribution; and finally, the anticipated life cycle of the therapy. The longer it takes the product to reach market, the longer the pay-back time.

Understanding the supply-demand price conundrum in the FVIII market

Jeffrey Stonebraker, University of Denver

Jeffrey Stonebraker commented that this is a difficult topic to comprehend, particularly for the FVIII market. In order to make key strategic business decisions, senior managers of pharmaceutical companies ask a number of questions:

- Do we develop this new product or not?
- If so, what size facility do we build?
- What is the optimum level of production capacity?
- Why invest all this capital into research and development when the manufacturers have already satisfied the marketplace? (The research could uncover a latent demand.)
- Why invest any more if the company has sold everything it has made?
- What is the real demand for FVIII?
- Can price erosion from increased supply render capacity expansion unprofitable?

Manufacturers face conflicting demands to meet patient needs and maximize profits. They have to find a balance.

Dr. Stonebraker showed a chart depicting the three intertwined objectives influencing the supply-demand-price conundrum: maximize profitability, maximize patient care, and minimize treatment costs. Supply issues include production capacity and regional allocation. Demand issues include historical sales, variability in epidemiology, treatment modalities, and supply constraints. Price issues vary according to product technology and by region. The definition of price is also important: Is price what the manufacturer pays, the wholesaler pays, the distributor pays, or the patient pays? Some stakeholders are only concerned with one of the objectives, while the trade-offs get complicated for those who are concerned with two or three objectives.

One way to decouple these variables is to model the triune relationship of supply, demand, and price. Dr. Stonebraker referred to a paper published in Haemophilia about unconstrained demand. How would physicians with all the supply they could ever want prescribe prophylaxis or ITI, for example? The model shows uncertainties such as price, demand, unit sales, competition, supply, and company plans. Both competition and the company's plans influence supplies. There is considerable variability in the process, which affects unit sales.

To make informed decisions about new products, most biopharmaceutical and biotech companies use a decision tree to examine new products. They start with strategic alternatives. There's a high barrier in the hemophilia market so there is a status quo option. The decision involves examining technical feasibility, which includes assessing the probability of technical success and commercial potential. The costs of goods and royalties contribute to the net present value.

Using a "tornado diagram," Dr. Stonebraker showed the key drivers of a new product development decision. Typically, pricing rises to the top. Technical success is also very important as are demand and supply. By changing the dial settings in the decision analysis model, a company can produce a histogram or a risk-return plot that depicts the payback for today's investment ten to fifteen years into the future.

In his final slide, Dr. Stonebraker described future research. An oligopoly—a situation in which few companies sell a similar product—has barriers to entry and is interdependent, like most biopharmaceutical companies. One definition of an oligopoly is to have four firms controlling forty per cent of the market share. An implication of this is price stickiness: competitors follow price cuts and tend to prefer non-price competition, which involves promotion, marketing, research and development, and product development opportunities. This may be a reason that prices tend to rise in different regions.

Overview of plasma economics

Jane Martin, Managing Director, Bio Products Laboratory

Jane Martin provided an overview of the fractionator industry with its dynamic market. Many factors in the market and the industry affect a company's product portfolio. Regardless of their size, all companies have the same common costs. The first of these is for plasma, which accounts for up to 60 per cent of product manufacturing costs. The heavy investments tied up in the fractionation process require ongoing capital investments to keep up with standards for licensing by the regulators. There are also costs associated with the regulatory considerations, risk assessment, quality systems, clinical trials for risk assessment, and getting supplies into the market. So, fractionators will have fixed costs roughly in proportion to their size.

Certain characteristics of the industry affect supply. Supply can be described as rigid and slow moving, while demand can be described as unpredictable and fast moving. Increasing the supply usually means increasing the production yield, which means investing in new technology, which takes both time and money. A major limiting factor is the supply of plasma: the raw material is limited, and all companies compete for it. These factors serve to cap production. As well, most of the plasma comes from the United States, so the economics of the supply are very important. The industry has high fixed costs and is concerned with economies of scale. The production cycle from plasma to finished product takes nine to twelve months, so the system is relatively inflexible and slow to change.

Each of the products from fractionation satisfies a different need and faces a unique demand driven by underlying factors that include healthcare budgets, funding systems, and the availability of substitutes. Clinicians' views on treatment, efficacy, and safety can have a profound impact on short-term demand for the product, and a long-term impact on a company's product portfolio. The discovery of new proteins and their mode of action also drives demand. Overall, these factors combine to create a volatile market in terms of both price and demand.

Ms. Martin used a series of slides to show how supply and demand for plasma products can change over time. When the supply of plasma is plentiful, its price decreases because it is a buyer's market. This leads to higher profit margins for the fractionation company, which in turn leads to more throughput and thus surplus proteins. When this happens, competition increases and price decreases, which reduces throughput. This leads to consolidation of plasma collections, which causes the plasma supply to become limited, which serves to increase plasma costs because it is now a seller's market. Profit margins decrease, global costs increase, the demand for plasma increases, and the cycle begins again with a plentiful supply of plasma. This cycle takes place over years, not months.

Investment decisions are based on many factors, including whether there is a global demand for a product. Regulatory, technical, and clinical trials all must be met successfully, with the latter often being the most difficult to achieve. Patents are another requirement as are sufficient time, corporate objectives, and adequate returns. Other coagulation factor products compete for investment with those of other companies, as well as with other plasma products.

One problem is that as cycles proceed, the market changes from being attractive to unattractive, and then eventually back to being attractive, said Ms. Martin. Where one is in that cycle influences decisions about how much to invest. This is a dynamic process with, on the one hand, a slow-moving industry that is unresponsive to change over the short term, and on the other hand, a fragmented market. When the two processes are out of balance, it is an unattractive industry to be in, but when they are in accord, the industry is much more attractive.

Is hemophilia care affordable? Perspectives on government and societal decision making in health spending

Albert Farrugia, Head, Blood and Tissues Unit, Government of Australia, ACT, Australia

Rather than providing a view from an industry perspective, as the previous three speakers have done, Dr. Farrugia said that he would provide the perspective of a government official who has a mostly peripheral role in influencing decision making in provision of resources for care.

Despite what many in the developing world assume, resource issues in the developed world are very important. Health care is increasingly becoming the focus of government political thinking. One of the main drivers of this is demographics: the rapid evolution of an aging population. The resources being spent on health care (including pharmaceuticals) are increasing. This is of immense importance, said Dr. Farrugia. It influences the way governments allocate resources and is a main driver of pubic policy.

Researchers such as Wolfgang Schramm have analyzed the cost-effectiveness of treatment for hemophilia care. Using FVIIa—"a notoriously expensive product"—as an example, Dr. Farrugia observed that the continuous pressure for funding for this product, despite the lack of clinical evidence for the increased indications, generates tension. "It has a lot to do with the money," he noted.

In Australia, the national blood authority includes funding for hemophilia products not derived from blood. The blood sector in Australia and in most other countries does not represent a big proportion of health care, so the question of the cost-effectiveness of blood is of supreme indifference to most people. Despite the fact that the cost of the blood system in Australia increased significantly in the last five years, it still represents less than 1 per cent of total health costs. In the United States, the proportion rises to 2 per cent.

In 2004, the Australian government decided to allow a policy of choice in product allocation for hemophilia treatment. This meant that recombinants were funded to the level that clinicians and patients wanted. The program budgeted $50 million annually and is currently costing $90 million, primarily because the consumption of FVIII has gone up significantly. Dr. Farrugia pointed out that there are very good clinical reasons for this as well as significant benefits for policy makers. There is now sufficiency in FVIII and a safer FVIII product. But one of the prime reasons for its funding was the protection of the politicians themselves following the judicial scrutiny of the hepatitis and HIV inquiries.

Dr. Farrugia noted that many societies, including Australia, have a rigorous framework for funding cost-effective healthcare interventions. However, hemophilia care and blood products are sheltered from this policy. Most healthcare interventions centre on the consideration of cost-effectiveness and economic parameters that include constructs such as quality of life.

A cross-section of Australians reported that they were willing to pay for healthcare interventions for people with high-cost illnesses in a minority of the population. An interesting caveat was that an exception could be made in cases where treatment costs were very high. It would be interesting, said Dr. Farrugia, to determine at which level people think a disease is too expensive. Surveys have also determined that people are far more willing to pay for treatment than they are to pay for prevention. A French study concluded that it was more cost-effective to not screen the blood supply for hepatitis C, but to treat the resulting cirrhosis in the general population and in transfusion recipients. However, screening was determined to be cost-effective in the intravenous drug-user population.

In conclusion, Dr. Farrugia said that the continuous obsession of policy makers with the cost of health care is not reflected in the kind of treatments that interest people with hemophilia. Much of the debate involving cost-effectiveness is probably outdated. Much of the criteria is being systematically misused by politicians as a way of cutting costs rather than allocating them on a rational basis. Many countries that are not as rich as Australia allocate hemophilia treatment because of societal pressures. However, the continuous expansion of healthcare costs, including for people with hemophilia, will be scrutinized by policy makers in the foreseeable future. The hemophilia community should be vigilant and concerned.

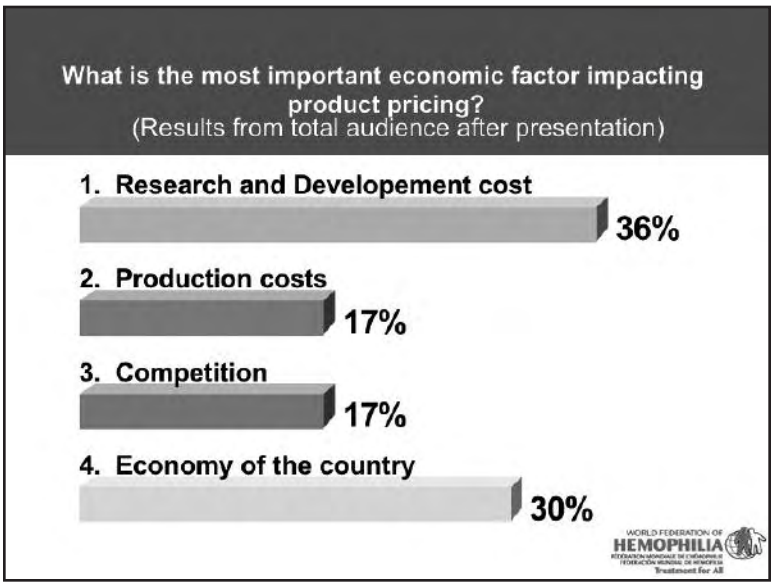
Discussion

The questions asked at the beginning of this session were repeated, although the second one was directed to buyers of the products.

Question 4 (repeated)

What do you believe is the most important economic factor impacting product pricing?

R&D costs	36% (30% first time)
Production costs	17% (15% first time)
Competition	17% (20% first time)
Economy of the country where it is being produced:	30% (34% first time)



Powerpoint slide from WFH Fifth Global Forum on the safety and supply of treatment products for bleeding disorders

Question 6

What do you, as buyers of these products, believe is the most important economic factor impacting product pricing?

R&D costs	17%
Production costs	6%
Competition	25%
Economy of the country where it is being produced:	52%

Glenn Mones, vice president for public policy, National Hemophilia Foundation (United States), noted that many of the changes in the industry are really reconfigurations. He asked panel members if they thought there would be further consolidation, if production capacity would change, and if the infrastructure would contract.

Paul Walton replied that he doubted that large-scale mergers, as seen in the past decade, would be approved now. Further consolidation would be limited by anti-trust considerations. Capital investment is not present for expansion. Instead, he predicted that the industry would concentrate on improving efficiencies and yields.

David Lillicrap said that some believe the hemophilia community is closing in on a paradigm shift—a cure for disease. He asked the panel members how they factor in the possibility of a cure in their business plans.

Jeffrey Stonebraker said that when he evaluates technology changes he would include significant developments such as gene therapy and the longer-acting recombinants as part of a company's competitive threats. That analysis could show that a company is too late to develop the next generation of a product given the competitive reality, or it could show that the investment is justified.

Albert Farrugia commented that it is obvious that intravenous immunoglobulin (IVIG) supports the plasma industry, which hopes there will not be a substitute for it. This profitability is a very good thing from the point of view of the hemophilia community because plasma concentrates and FVIII are still needed. The environment is very different today than it was 15 years ago when FVIII was "the biggest slice of the pie."

Raymond Stanhope, Chair of the Board, National Hemophilia Foundation, said that it was interesting to see the different views of the consumer versus manufacturer on the R&D costs. He asked if the panel members thought that R&D costs would go to zero in a given generation of a product.

Dr. Walton replied in the negative. Dr. Farrugia said that the percentage of R&D costs normally quoted by industry does not reflect reality. He contended that the emphasis on R&D is exaggerated. He has seen product improvements and modifications for plasma derivatives, but no significant new products during his career. This is a stable, conservative industry. Over the years many putative new products that promised to treat all manner of new diseases have not been realized.

Question 7
Do you believe that biosimilars for clotting factor concentrates could be viable? Both regulatory approval and economic viability.

Yes, in 5 years	19%
Yes, in 10 years	41%
Yes, in 15 years	26%
Never	14%

Biosimilars: Regulatory issues

Sol Ruiz, Head of Biotech Division, Spanish Medicines Agency

Sol Ruiz noted that in Europe, biosimilars are limited by the techniques available to discern the subtle differences and their sensitivities, by current knowledge of the product, and by the ability to determine if these differences have an effect on the efficacy and safety of the product.

Due to its complexity, the quality of a biological product is determined by a combination of physicochemical and biological testing, together with the production process and its control. Bioactivity and immunogenicity are dependent upon its structural features. By contrast, a chemical product has a well-defined molecular structure that is easy to characterize, an impurity profile that is dependent upon the synthetic and degradation route, and safety and efficacy that are independent of the origin of the product.

Recombinant products have proteins and glycoproteins. Some, such as FVIII have large complex molecules and an inherent microheterogeneity due to post-translation modification, from which glycosylation is the main one.

Novel sources of recombinants, such as transgenic goats, are now a reality. Last year the EU licensed a recombinant product—a human protein—extracted from the milk of transgenic goats. Companies are trying to license different products such as antibodies from plants. Both provide challenges for quality control; comparability studies require a new market authorization that compares this new product to a reference product.

A comparability study is controlled in Europe by a guideline that addresses changes in the manufacturing process. The extent to which a study demonstrates comparability will depend on a number of factors, including the production step where the changes are introduced; the potential impact of the changes on the purity and the physicochemical and biological properties; the availability of suitable techniques to detect product modifications; and the relationship between quality attributes and safety and efficacy.

With the new situation—the new marketing authorization and comparison to an existing product—a comparison based on a pharmacopoeia monograph is not sufficient, said Dr. Ruiz. Independent development will result in inherent differences in the following:

- source materials, expression systems, and culture process details (even with the same cell line, the cloning procedure and culture process will be different);
- purification processes (scheme, scale, operation); and
- in-process controls, test methods, and specifications.

Dr. Ruiz described a typical purification process for a biotech product, which includes a number of chromatography steps and in-process controls. Some of the impurities detected by testing during the purification process are present in such minute quantities that it would be impossible to spot them if testing were left until the final product was produced.

The International Conference on Harmonization (ICH) quality assurance strategy sets specifications for the safety and efficacy of biotech products based on a number of parameters: in-process controls, stability studies, process validation, control of starting materials, extensive characterization during the development of the products, and good manufacturing practice (GMP) compliance. New clinical studies will be needed for a new product depending on the nature of the drug substance and formulation, the complexity of its molecular structure, and the differences between it and the reference product. In the EU, similar biological medicinal products must have the same pharmaceutical form, dose, and route of administration as the reference product, and there can be no extrapolation between different administration routes. The reference product should be the same throughout the dossier and it should be available in the EU. There should be preclinical comparative studies in vitro and in vivo for pharmacokinetics, pharmacodynamics, immunogenicity, and toxicity. There should also be efficacy and safety data showing comparability, and studies for immunogenicity, a pharmocovigilance system, and a risk management plan. This represents a big difference vis-à-vis generic products.

For new manufacturing processes, the EU has guidelines on quality issues and on clinical and non-clinical issues. The EU has approved several biosimilar products, two of which are growth hormones. To illustrate how products can differ when manufacturers switch from one production site to another, Dr. Ruiz noted that analysis of these products revealed that although the spectrometric, sequence data, and physicochemical data did not reveal significant differences, the material produced at the first site contained a significantly higher amount of host cell proteins (HCP) than the material produced at the second site. The material from the first site was determined to be significantly more immunogenic in patients (57% versus 2%) and will not be commercialized. Further studies determined that the formation of anti-GH antibodies was most likely related to the presence of an increased level of HCP proteins, but that these had no effect on efficacy.

In closing, Dr. Ruiz noted that much of this information is available on the European Medicines Agency (EMEA) website (http://www.emea.europa.eu/). New versions of the guidelines for human plasma-derived FVIII and IX products and recombinant FVIII and IX products are being developed.

Scientific considerations for the development of follow-on protein products

Mark Weinstein, Office of Blood Research and Review, Center for Biologics Evaluation and Research (CBER), US Food and Drug Administration (FDA)

Mark Weinstein commented that since the FDA's policy regarding the development of these products is a work in progress, he would discuss their scientific considerations and current regulatory perspectives.

Janet Woodcock, deputy commissioner, FDA, first used the informal term "follow-on protein product" when she testified before a congressional committee earlier this year. She defined it as proteins and peptides sufficiently similar to an approved product to permit the applicant to rely on certain existing scientific knowledge about the safety and effectiveness of the approved protein product. In other words, one can submit an application that contains material about an approved product's safety and efficacy that can be applied to a biosimilar. In addition, however, further medical safety information for the biosimilar will be required. A follow-on protein product may be produced through biotechnology or derived from natural sources.

Under the US Food, Drug, and Cosmetic (FD&C) Act section 505(j), the active ingredient in a generic drug is an exact duplicate of an already approved drug. The sponsor has to demonstrate that it has pharmaceutical equivalence, the same active ingredient, the same dosage form, the same route, and the same strength as the approved product. It also has to have the same bioequivalence—the same rate and extent of absorbance and the same availability at site. In other words, it has to have the same pharmacokinetics and pharmacodynamics as the approved product. If the sponsor can show that it has the same pharmaceutical equivalence and the same bioequivalence as the approved product, no clinical or pre-clinical studies are required, and it may be possible to get the product approved for therapeutic equivalence. This means that at least in some states, the generic drug becomes interchangeable with the approved drug: a pharmacist can make the exchange without the intervention of a physician.

The approval of a follow-on protein product has an abbreviated application under the FD&C Act. It relies, to some extent, on the Agency's conclusions regarding the safety and effectiveness of an approved product. The application must also have additional data that establishes that the follow-on product is safe and effective.

Drugs and biologics do not currently fall under the FD&C Act, but rather come under the Public Health Service (PHS) Act. A biological product is defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product…." It is complex though, said Dr. Weinstein: there are overlaps between chemical drugs regulated under the FD&C Act and biologic or biotechnological proteins regulated under the PHS Act. Under the parameter of manufacturing, a chemical drug has a predictable synthetic pathway with defined composition in contrast to the inherent heterogeneity that exists in the biologic or biotech proteins. One can easily define the structure of a chemical drug, while biological material is very complex and difficult to characterize. For bioactivity, a chemical drug has a defined single activity. In contrast, a biologic product such as VWF has multiple activities and multiple differences that are difficult to assess. There are defined standards and specifications for impurities of chemical drugs, but biotech products can have minute impurities that drastically affect the safety of the product. Regulators are also concerned about the potential for infectious disease from biological products.

Dr. Weinstein briefly addressed some of the challenges involved in comparing a new product with an approved one. As an illustration, he showed a simple product, a statin, with a relatively small molecular weight of 400 Daltons, compared with immunoglobulin Fab fragment, which has a molecular weight of 50,000 Daltons. In addition, there is a tremendous difference in the size of the proteins, and the structural features are quite dissimilar. It is relatively easy to look at the primary structure of a protein, but quite difficult to look at how it is folded into its secondary, tertiary, and quaternary structure. However, new methodologies, techniques, and instrumentation being developed may permit better analysis of materials. Post-translational modifications are a concern. The various recombinant materials in some FVIII proteins each have a different molecular weight and heterogeneity. What then does one compare a new recombinant product to with respect to the approved product? No one knows if one or more of these products is the same with regard to immunogenicity.

The final slides that Dr. Weinstein presented showed the FDA's decision-making process. The more knowledge that is available about the approved product—its mechanisms of action, structure, and function, and its clinical experience, adverse events, and end points—and the greater the similarity and the smaller the complexity, the less researchers have to ask for additional studies for the safety and efficacy of the follow-on biological.

Canadian regulatory perspectives on biosimilars

Anthony Ridgway, Senior Regulatory Scientist, Biologics and Genetic Therapies Directorate, Health Canada

Anthony Ridgway said that regulators first look at the comparability of products. This not only concerns the chemical structure of the product, but also the relevance of its clinical data. The drug substance of a drug product has to be evaluated in a process step most appropriate to detect a change in the quality attributes, and this may entail evaluations at multiple steps of manufacturing.

The ICH provides a number of quality guidances for comparability. Key elements for demonstrating comparability are characterization, specifications, and validation. Characterization should include chemical structure, physiochemical properties, biological activity, purity, impurities, and quantity.

It is important to note that a biological property is actually a mixture. A drug substance is made up of multiple entities, including the substance that is actually being sought—the desired product (which can be microheterogeneous). In addition, there can be product-related substances, product-related impurities, process-related impurities, and contaminants. When undertaking a manufacturing change it is important to cover off all possibilities, and remember that regardless of the extent of planning, something can always go wrong. Therefore it is important to include tests specifically directed at fully evaluating the impact of the change on the product.

Even if the comparability is strong from a quality perspective, regulators may still want clinical data. Usually this is involves a smaller bridging study. Clinical considerations include indication, dosing and patient response, and safety versus efficacy. In the area of indication, mode of action is important. Many concerns today focus on safety and immunogenicity.

Most biopharmaceuticals induce antibodies. Manufacturing changes can cause unsuspected changes in immunogenicity. Unfortunately, current analytical methods cannot fully predict biological properties, so the immunogenicity of biopharmaceuticals may have serious clinical consequences.

The demonstration of comparability within a product change in manufacturing means that the quality attributes of the post-change product are highly similar to those of the pre-change product. The pre-clinical and clinical data obtained with earlier versions of the drug product are relevant to the post-change product. The manufacturing changes do not have an adverse effect on the quality, safety, or efficacy of the drug product. For biosimilars, this translates into extensive studies on a suitable comparative. However, virtually everything in the manufacturing of the follow-on product has changed, so the challenges can be significant.

Dr. Ridgway described some of the challenges involved in comparing a biologic with a chemical drug. These include the size and complexity of the "desired product," its heterogeneity, the possible presence of adventitious agents, limitations of methods for characterization (although these are improving), and immunogenicity. Innovators have tremendous advantages when trying to demonstrate comparability for their own product compared with what the manufacturer of a biosimilar goes through.

There are clear challenges with respect to the generation of biosimilar products and clinical data. How can one ignore a putatively highly similar product that has been used in millions of patients over the previous 15 years or longer? How does one translate that information into a reasonable regulatory decision? Clinical data has to be included in the dossier. It could be generated from brand-new studies, but if those studies are as expensive as they are for the innovators, that will place a severe limitation on the ability to produce biosimilars. It could come from information published in scientific journals relative to the comparator. There may also be a place for the application of a regulator's experience including proprietary sources.

The regulatory pathway approach and set of requirements for less complex products will be inadequate for complex products and vice versa. Clinical parameters will influence data requirements. Therefore, detailed guidance must be specific to product or class and the regulatory approach will have to be on a case-by-case basis. In closing, Dr. Ridgway noted that regulatory decisions on biosimilars are possible in Canada within the scope of current regulations. The issue of whether the comparator needs to be Canadian is under "intense internal discussion" at Health Canada. One indication will not support all indications, but with the same mechanism of action and a strong rationale, it may be possible to have an additional indication without the same amounts of clinical data. It is Health Canada's opinion that these products should not be interchangeable or substitutable.

Could plasma concentrates be considered as generic/follow-on/biosimilar drugs?

Albert Farrugia, Head, Blood, and Tissues Unit, Government of Australia, ACT, Australia

Albert Farrugia noted that his interest in this topic stems from his desire to make regulation applicable to less developed environments. Regulatory requirements that are applicable in the developed world in relation to certain key issues (particularly around plasma concentrates) make the product very difficult to obtain by emerging companies in the developing world. There is no question of taking shortcuts: the focus is on the question of clinical development. Also, the primary issue behind the debate about biologicals relates to immunogenicity.

On the whole, Dr. Farrugia agreed that biologicals are complex, therapeutic goods. However, he suggested that notion not be "pushed too far." An earlier speaker noted that FVIII has six manufacturing steps, but some organically synthesized pharmaceuticals

have 50. Many of the plasma concentrates still on the market from the previous generation have been minimally reviewed by regulatory agencies. Many of the guidances have not been applied to these products, which were "grandfathered."

Dr. Farrugia noted that it is not possible to derive much abbreviation of the regulatory path for recombinants. A plasma-derived concentrate could be a new product that might be a modification of an existing manufacturing method, but it is not possible to demonstrate efficacy or safety sufficiently without clinical trials. "Copied" products may be very similar to an existing product, but they require clinical trials to verify—not establish—efficacy. This is an important distinction.

The more interesting issue for this community (and particularly for emerging countries), said Dr. Farrugia, is the product produced under licence or technology transfer. Brazil, which has a project involving a technology transfer path to a fractionation capacity, has to decide if it should access a clinical trial validation pathway that is equivalent to that demanded for the original site. This might not be the case. Dr. Farrugia said that when his agency has a change of site for a manufacturer, it does not require clinical trials if there were adequate demonstration of pharmacological equivalence. He therefore proposed that a real technology transfer with absolutely seamless passage of methods of manufacture is no different from a change of site.

The question of immunogenicity cannot be satisfactorily assessed with preclinical trials. Emphasis should be placed on post-market surveillance (when most problems become evident), not on developing an expensive infrastructure for phase 3 studies in centres of excellence, which do not generate predictive information.

The mechanism of pdFVIII is well understood, said Dr. Farrugia. Sometimes it is manufactured using well-established methods. Many fractionators are careful with the processes in relation to deriving higher yields. Most of the time it has a well-established safety and efficacy profile. "We know pretty well what kind of clinical response to expect from pdFVIII," he said. Therefore, in some instances, it should be possible to gain an appreciation of the manufacturing process and allow it to enter the market without the very sophisticated, complex, and expensive clinical trial infrastructure of the developed world. Dr. Farrugia said that he was not advocating for a total removal of requirements; rather, he believes it should be possible to design some abbreviations. The process is difficult and expensive, and, even in the developed world, the community is running out of patience with this full-scale range of studies.

When products are manufactured using well-understood methods, their physical and chemical characteristics have a reasonable level of consistency. Using the regulatory path for AHF (high purity) in Australia, Dr. Farrugia recalled that the product was in fact identical to BPL's 8Y by licence, and put on the market in 1989. When his agency was established in 1992, the product was grandfathered. When the manufacturer moved its facility from its plant in Melbourne to its plant in Broadmeadows, this change of site afforded the opportunity for review. Information on clinical experience was added to the information on the parent product for viral safety. This product was withdrawn from the Australian market in 2003, and replaced with a totally new pharmaceutical that had a totally new method of manufacture. The government conducted a full pre-market review, including clinical trials. For a reasonably well resourced first-world environment, this model is possible.

Dr. Farrugia said that when he hears arguments against the concept of "genericity" in biologicals and biosimilars, this is one area in which regulators and large pharmaceutical companies are in alliance. Their reservations are generally justified for highly technologically advanced biotech-based coagulation factor concentrates. He sees no room for

abbreviation from established methods for recombinant-type products and even for some plasma-derived FVIIIs if the technology is not good enough to justify it. Technology transfer agreements, such as the one in Brazil, should allow for an abbreviated regulatory path for clinical validation. There should never be an abbreviation on clinical chemistry manufacturing and controls, standards, or good manufacturing processes.

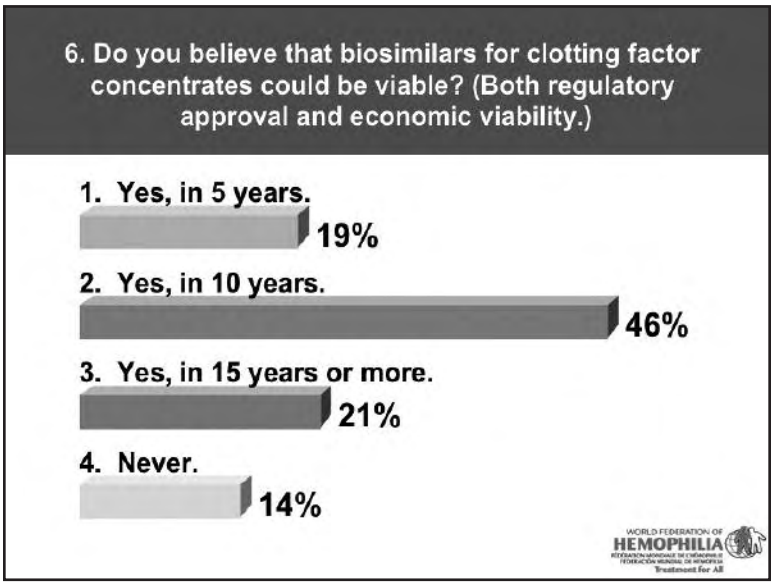
Discussion

The question that launched this session was repeated:

Question 7 (repeated)

Do you believe that biosimilars for clotting factor concentrates could be viable? Both regulatory approval and economic viability.

Yes, in 5 years	19% (19% first time)
Yes, in 10 years	46% (41% first time)
Yes, in 15 years	21% (26% first time)
Never	14% (14% first time)



Powerpoint slide from WFH Fifth Global Forum on the safety and supply of treatment products for bleeding disorders

A participant asked if and when it would be possible for regulatory authorities in Europe, Canada, the United States, and Australia to develop a harmonization process for licensing biosimilar products.

Mark Skinner replied that he did not foresee the status quo changing quickly. Dr. Ruiz concurred, noting that even within the EU, companies have to apply to the different countries. Work is underway on a database of clinical trials, but Dr. Ruiz predicted that it would be some time before one sees harmonization.

Dr. Ridgway also agreed, commenting that in Canada, the Minister of Health is responsible for approving products. Nothing in Canada's Food and Drug Act permits a foreign designation or acceptance to override this legal accountability. In addition, there are barriers around proprietary information and intellectual property. He conceded, however, that it would be helpful to have a consortium of like-minded regulators look at this using a consensus approach.

Dr. Farrugia replied that it is not reasonable to expect the regulatory community to be at the forefront of harmonization. Regulators are essentially functionaries of the political process, and politics has proven to be a stumbling block. The electorate in most countries want their politicians to be accountable for decisions. There are initiatives underway, but Dr. Farrugia, too, predicted that harmonization would be a long time in coming.

National tenders update

Chair Brian O'Mahony, President of the Irish Haemophilia Society, opened the session by polling participants from various sectors on the same question.

Question 8: All answer

Four companies compete for a national FVIII tender. Which is the best outcome?

One company supplies all	3%
Two companies share	24%
Three companies share	19%
Four companies share	4%

Question 9: Only manufacturers answer

Four companies compete for a national FVIII tender. Which is the best outcome?

One company	11%
Two companies	38%
Three companies	11%
Four companies	40%

Mr. O'Mahony noted that several points must be considered in discussing national tenders, including selection criteria, optimizing tenders, determining whether tenders are the best method for procuring supply, and patient involvement.

He outlined the scoring criteria used for two recent tenders for FVIII and FIX in Ireland. Tenders were scored on safety, efficacy, quality, supply security, scientific support, and cost. However, because of the relative weighting system used, cost only accounts for 10 to 15 per cent of the total score. Safety is most heavily weighted, accounting for 44 per cent of the score, while efficacy accounts for 17 per cent and quality 22 per cent.

He noted that price would undoubtedly be a more significant factor in countries with lower GDP, but stressed that cost should never be the only criteria.

The experience in Thailand

Sorakij Bhakeecheep, National Health Security Office, Bangkok, Thailand

Sorakij Bhakeecheep shared Thailand's experiences with national tenders for the procurement of factor concentrates and also presented another method for a unified procurement system, a "single-price system that might be useful for other nations putting out a national tender."

In 2004, the national hemophilia society in Thailand became involved in the WFH Global Alliance for Progress (GAP) program, whose goal was to achieve a national hemophilia

program for Thailand. The program was organized by an alliance of four organizations and had the following objectives:

- Improving quality of life
- Increasing the quality of care
- Reducing mortality and morbidity

Because Thailand is a developing country with limited resources, Dr. Bhakeecheep said, procuring an adequate supply of treatment products at an affordable price was a challenge. To address this problem it was determined that a unified national procurement system was needed, which led to the development of a national tender. A committee was struck to oversee the tender. It consisted of seven representatives from the National Health Security Office (NHSO) and two technical advisors from the National Hemophilia Federation of Thailand (NHFT). The goal was to achieve a price of US$0.16/IU. The first national tender in January 2006 was for 20 million units of FVIII. The second, in February 2006, was for 10 million units.

The tender criteria take safety, quality, and efficacy into account, he said, using a set of product characteristics developed with the assistance of the technical advisors on the tender committee. Of the products that meet the criteria, the lowest price was accepted. This might not result in procuring the best product, but it did succeed in getting an adequate affordable supply.

Dr. Bhakeecheep noted that before the national tenders, the market price for factor was approximately US$0.40/IU. After the tenders, that was cut in half to US$0.20/IU. The expected price had been US$0.16/IU, but it rose slightly due to a supply shortage.

After these tenders, he continued, the strategy was changed to a central purchasing system using central bargaining, but local purchasing. Instead of buying in bulk and distributing factor concentrates to hemophilia centres, individual centres are allocated budgets and purchase their own factor using a single-price system, arrived at through a multiple negotiated tender.

With good collaboration between pharmaceutical companies and the hemophilia centres, the single price system has been a success, he said. Both doctors and patients appear to be satisfied. However, he noted that the price (US$0.20/IU) began to rise somewhat after five months, due to global supply issues. Though, at US$0.26/IU, it is still well below the market price before the system was put in place.

Dr. Bhakeecheep said Thailand learned several important lessons during its national tenders:

- National tenders may not always be the way to get optimal outcomes
- Open price negotiated tender avoids monopoly and allows for fair competition in the market
- Big lot purchasing does not always yield the lowest price, particularly in light of additional administration expenses, stocking, cold room storage, and logistics
- Allocating budgets directly to treatment centres encourages effective drug utilization and broader patient participation
- Negotiated tenders can achieve prices as low as national tenders

He concluded by encouraging other countries to consider negotiated tenders and other locally customized solutions when designing procurement strategies.

Brazil

Sylvia Thomas, President, Brazil Hemophilia Society

Sylvia Thomas began by explaining that Brazil is a huge country, with the second-largest population in the Americas and the third-largest population of registered hemophilia patients. The Brazilian constitution guarantees every citizen the same right to public health. That means that every person with hemophilia in Brazil has the right to receive factor products free of charge.

Hemophilia care is the responsibility of 32 hemophilia treatment centres located across the country. The majority of registered hemophilia patients are in the southeast region, near Sao Paolo and Rio de Janeiro. Doctors are not allowed to prescribe cryoprecipitate or plasma for hemophilia or VWD patients, so treatment is limited to factor concentrates. Factor usage is 1.25 IU per capita and most treatment is on demand. Access to home treatment exists, as well as short secondary prophylaxis, but only if supplies permit. Primary prophylaxis is not available nationwide.

The Ministry of Health has a two-tiered tender committee model, where the administrative committee acts on the advice of a technical advisory group. Of the six members of that advisory group, there must always be a consumer representative and, usually but not always, a physician.

National tenders for procuring factor were established in July 2002. Information about the tender system, which is called PREGÄO (the Portuguese word for "reverse-auction") is public and can be accessed openly on comprasnet, the e-procurement system established by the Brazilian federal government, Dr. Thomas explained.

The government of Brazil says it has saved over US$350 million since it instituted the national tenders for factor in 2002. Unlike the scenario that Mr. O'Mahony outlined in Ireland, Dr. Thomas said that cost is the most important factor in Brazil's national tender. However, there is also very careful adherence to the terms of reference established by the technical advisory group. She said this model could be used by other developing countries where cost is a major consideration.

There are some problems with the system, though. Dr. Thomas said Brazil is particularly sensitive about the possibility of corruption as the result of a scandal involving the purchase of factor concentrates that was called "vampire selection." Companies made agreements to share the market, which resulted in an average factor cost of US$0.40 per unit. In response to this scandal, procedures were put in place that makes the procurement process much slower.

There are also legal constraints against buying factor from multiple suppliers, she said. Given the enormous amount of factor purchased, finding a single supplier is extremely difficult, so there are frequent shortages. Ways of addressing these problems include contract fractionation, a national fractionation plant, or changing to the tendering process.

Octapharma won the contract fractionation bidding process, which will help resolve some of the supply problem she said. Despite attempts to dissuade them, the government is also going ahead with plans to open a national fractionation plant that will produce FVIII, FIX, albumin, and IVIg. The plant is scheduled to open in 2010 and its goal is to fractionate 450,000 litres of plasma from its fifth year of production onward.

It has been impossible to buy the necessary amount of factor from a single supplier in recent years, Dr. Thomas said. Each time there is a supply shortage, the government orders the suspension of elective procedures and home treatment. She said this is an unacceptable solution that results in increased mortality and morbidity.

Therefore, the Brazil Hemophilia Society is seeking international cooperation and the participation of treaters and consumers in helping review the laws regarding national tenders. It is unacceptable not to have adequate supply to treat patients because of a set of regulations that are unrealistic. She invited the help of the international community to try to change some of the rules, so that the system can be transparent, ethical, and respectful of Brazil's laws, without leaving the population with frequent treatment product shortages.

United Kingdom

Paula Bolton-Maggs, Consultant Haematologist, Manchester Comprehensive Care Haemophilia Centre, Manchester Royal Infirmary, Manchester, UK

The usage of FVIII has progressively increased in the UK to the point that, in 2005, 330 million units were purchased, Paula Bolton-Maggs explained. There are 27 comprehensive care centres in the country and 67 smaller centres that dispense recombinant products. In total, there are approximately 5,000 people with hemophilia in the country, 2,200 with severe hemophilia.

The Department of Health has worked with the doctors' organization, the hemophilia society, and local health systems (primary care trusts) to agree to a strategy for a national tender, she said. Because of the excellent hemophilia reporting system, the number of patients, distribution of purchasers, quantity of products used, and expenditure on products is known. This detailed background information makes a sophisticated procurement process possible.

National tendering is intended to bring the price down, Dr. Bolton-Maggs said, but also to improve supply reliability, reduce workload for purchasers, and allow clinicians to drive the process. Clinicians in the UK have noted that switching from plasma-derived to recombinant products has not increased inhibitors, which has led to an increasing acceptance of switching. And there is general consensus that all recombinant products are comparable.

The Commercial Directorate is responsible for adopting commercial practices that enhance the efficiency and effectiveness of the National Health System (NHS). Savings on some pharmaceutical products over the last three years have been as high as 20 per cent, with a 7 per cent reduction in costs across the board, she said.

The UK pays the highest average prices for concentrate, Dr. Bolton-Maggs said. The Commercial Directorate examined international prices for factor concentrates and determined that £55 million could be saved if factor could be procured at the international best price, £40–45 million if the US best price was matched, or £24–28 million if all products could be bought at the UK best price.

The health department surveyed extensively to determine what existing structures could be used to develop existing local or regional arrangements, and determine the degree of support for a national arrangement, as well as the major impediments to accepting such an approach. After extensive consultation, the Commercial Directorate developed a procurement strategy that would achieve price harmonization and reduction through volume concentration. The tenders were awarded after two procurement waves to minimize risk, while maintaining supplier interest.

Dr. Bolton-Maggs outlined the criteria and weighting for bids assessment:

- Safety 25%
- Efficacy 20%
- Organizational Fit 5%
- Supply Security 10%
- Price 40%

The national purchase system that was developed is an e-auction, which asks companies to offer a price for a particular portion of the market. Bidders were asked what their best price would be if they had the whole market, if they had half the market, if they had 20 per cent of the market, and so forth. After this process, Deloitte was brought in to set up and evaluate different models, so that individual centres could decide their own split of products. The system worked well for the recombinant rollout, so the same approach was used for the second wave of procurement. As a result of this approach, there were large shifts in market share for particular companies and 20 per cent of patients (mostly adults) changed between recombinant products. And, Dr. Bolton-Maggs noted, £55 million in savings was achieved.

There were several keys to the success of the UK tenders, Dr. Bolton-Maggs said. Years of regular data collection and a comprehensive national database were already available. The involvement of Deloitte allowed the maximum cost-benefit and a cohesive group of clinicians were involved in every stage of the process.

A manufacturer's view

Sophie Ludgate, Director of Government Affairs & Public Policy, BioScience Europe, Baxter

Noting that her comments were only meant to reflect the views of the company for which she worked, Sophie Ludgate said that Baxter was committed to clinical freedom in hemophilia treatment defined by patient need, where treatment regimens were chosen by doctors in concert with patients. In addition, she said, the company supports purchasing processes that acknowledge the clinical differences in therapeutic options and recognize research and innovation. Acknowledging that national tenders are increasingly a reality in the provision of hemophilia treatment products, she said there are pros and cons in using them for procurement.

Whether tenders will be beneficial or detrimental for hemophilia treatment depends on the existing standards of care for hemophilia treatment in a particular country, what the motivation is for introducing a tender, and how the tender is conducted, Ms. Ludgate said. Tenders can be a positive force for improving care in developing countries where they can help influence governments to introduce care or increase the standards of care by allowing control of price and supply. However, in developed countries the motivation for introducing tenders is usually control. As a result, the process can lead to a number of possibilities:

- Limitations on clinical freedom
- Limitations on the opportunity to increase prophylaxis
- Limitations on access to new therapies
- Treatment caps

Ms. Ludgate said the tender's impact will be determined by the nature of the tender and how it is developed. Often, tendering processes are not clear and transparent. Baxter supports processes that use a single tender committee with a full range of appropriate parties represented, particularly clinicians and patients. The committee should also include relevant health department and regulatory officials. She also supported comprehensive weighting criteria. While the opinions of those polled at the Forum clearly established safety as the most important factor in choosing treatment products, most of the tenders discussed weighted cost as the most influential component of a bid.

Ms. Ludgate suggested that e-auctions are not the proper modality for procuring hemophilia treatment products. Factor concentrates are lifesaving treatments that are extremely difficult to develop, manufacture, and distribute. They should not be treated like basic hospital supplies. The auction process eliminates dialogue between patients and clinicians. This is particularly problematic in countries that, unlike the UK, lack accurate and comprehensive bleeding disorders databases. Widespread use of the e-auction process could threaten future innovation, she said.

Ms. Ludgate concluded by stressing that payers should not be making clinical decisions and that the bleeding disorders community should be wary of the motivation for tenders in some countries. In the event of a tender, she said, it is crucial that there is expert clinical and patient involvement at every level and that the process is fair and transparent.

Discussion

Albert Farrugia stressed that a successful tender process must yield a multiplicity of products.

Paula Bolton-Maggs replied that the UK had not seen a higher risk of inhibitors when switching from high-purity FVIII to recombinant products. She also noted that avoiding product switching has become less important, but the need to have multiple suppliers to avoid shortages has increased.

Brian O'Mahony observed that, although local hospitals make the choice from a list of available products, there's still a high premium on clinical freedom. The presence of clinicians and patients on the tender committee, however, gives them strong clinical input, even though some freedom is sacrificed.

Wolfhart Kreuz asked if there was any explanation for recent findings that saw elderly hemophilia patients in the UK with more than 200 treatment days developing inhibitors at rates over 6 and 7 per cent, when normally the rate is 0.2 per cent. Dr. Bolton-Maggs said she was not familiar enough with the data to offer an explanation, but offered to take the question back to her colleagues.

A participant from Russia asked for details of how the cost of logistics and distribution were factored into a tender. In Brazil, Sylvia Thomas said, the cost of logistics and distribution is excluded from the tender and is the responsibility of each state. In the UK, agreements about budgets are devolved to the local purchasers, according to Dr. Bolton-Maggs.

Mr. O'Mahony observed that in EU countries, pre- or post-tender price negotiations are not allowed. In Thailand, however, the same restrictions do not apply, according to Sorakij Bhakeecheep. There the price is set according to "the reality that the pharma companies can provide."

Sophie Ludgate noted that, from a manufacturers' viewpoint, it is important that the process not change halfway through, which can lead to product shortages.

Alessandro Gringeri expressed reservations about the tendering process in developed countries where they are a mechanism for saving money. Saving money usually means minimization of costs, not necessarily cost-effectiveness or cost-benefit analysis. With tendering processes, there are sometimes caps put on the amount of product that can be used. In some countries, tenders are the only way to ensure sufficient product availability to start treatment programs, he conceded. However, in others their only goal is to save money. Freedom in choosing products and therapeutic approaches should be guaranteed wherever possible.

Dr. Thomas disagreed that treatment goals were different in developing countries. Poorer countries also want prophylaxis, immune tolerance therapy, and access to adequate products. Even in rich countries like the US, there is not real freedom because the system is private. Choice is not a straightforward issue as long as treatment is not available equally to all patients.

Mr. O'Mahony said there is a danger that the tendering process can limit clinical options. He reiterated the importance of involving clinicians and patients in the process and ensuring that selection criteria deal with quality, safety, and efficacy, in addition to cost.

Dr. Bolton-Maggs questioned why there was such a huge variation in prices for the same products. The goal in the UK was to bring all prices down, she said.

Dr. Farrugia expressed apprehension about agreements between government compelling open competitions involving tenders, noting that the phenomenon of low prices for developing countries was a recent one and stressing his "fervent hope" that it be sustained.

Chair O'Mahony re-polled participants on questions regarding pricing.

Question 10: for patients and NMOs only

Do patients benefit from national tenders for clotting factor concentrates?

Yes	61%
No	22%
Don't know	17%

Question 11: for regulators/ governments only

Do governments or other purchasers benefit from national tenders for clotting factor concentrates?

Yes	81%
No	11%
Don't know	8%

Question 12: for manufacturers only

Do manufacturers benefit from national tenders for clotting factor concentrates?

Yes	27%
No	54%
Don't know	19%

Question 13: for clinicians only

Do clinicians benefit from national tenders for clotting factor concentrates?

Yes	47%
No	46%
Don't know	6%

Roundtable: Impact of longer-acting clotting factor concentrates

New treatments for hemophilia

Glenn Pierce, Vice President, Preclinical Development, Bayer HealthCare

Glenn Pierce provided an update of Bayer's new therapies for hemophilia, particularly in two areas: work with collaborators on FVIII formulated in PEGylated liposomes, and pre-clinical development with PEGylated FVIII (Kogenate-N or KG-N).

When existing FVIII is diluted into a PEGylated liposome solution, it will not covalently attach to the PEG on the outer surface of the liposomes. This provides for a unique drug combination that prolongs the activity of the FVIII. Bayer attached low quantities of polyethylene glycol to liposomes with the goal of providing week-long protection. The FVIII combined directly to the polyethylene glycol, making a complex referred to as KG-Lip.

There are many precedents for working with these molecules, said Dr. Pierce. Polyethylene-glycol drugs and liposomal drugs are safe, effective, and licensed for other indications and diseases. In vitro data shows that FVIII attached to PEG-Lip is fully active, and that liposomes do not alter the interaction between FVIII and its carrier protein in the circulation or in in vitro clotting assays. Recoveries are comparable with intact FVIII. A hemophilia mouse model demonstrated prolonged survival with KG-Lip relative to rFVIII. A preformed complex is required: if the mouse is injected with a PEGylated liposome separately, there are no advantages to the therapy.

Based on these results, Bayer initiated clinical studies. Phase I studies showed that the single infusion of KG-Lip was well tolerated. Two clinical efficacy studies suggest that there are advantages to using the KG-Lip over using Kogenate FS. A recent infusion rate study showed that this was safe and well-tolerated when given as a five-minute infusion, as is standard in home treatment. This has set the stage for a much larger multinational study that is about to begin.

The first efficacy study of the post-infusion prolonged bleed-free interval showed a statistically significant increase in the number of bleed-free days and an advantage to using KG-Lip over using Kogenate alone.

The National Hemophilia Foundation recommends maintaining FVIII trough levels at greater than 1 per cent of normal for prophylactic treatment. Increasing the dose will have a minor effect; therefore, the approach is to increase the half-life of FVIII. The focus of this project is to improve the FVIII pharmacokinetic profile while still maintaining efficacy, thus allowing for weekly dosing.

Because the FVIII molecule can bind to FIX and FX and VWF, and is able to attach to activated platelets, site-specification PEGylation is required. In many respects, this is an empiric exercise, noted Dr. Pierce. One has to make and test many constructs to find the right molecules.

Bayer has examined the pharmacokinetics of a PEG construct termed A3. Compared with the domain-deleted version of FVIII, there is an increase in the recovery of FVIII activity throughout the 24 hours studied. Therefore, it achieves a long plasma residence life for PEGylated FVIII.

In the Tail Clip Model (TCM), hemophilia A mice are treated either acutely—right before the injury—or 20–48 hours before the tail amputation. In the Tail Vein Transection (TVT) Model, some of the mice's tail veins are clipped one to four days after infusing with either FVIII or PEGylated FVIII molecules. This better mimics the kind of bleeding characteristic in hemophilia, noted Dr. Pierce.

Each of the four PEGylated constructs in the TCM increases the protection compared with that afforded by the two parent molecules, but by different amounts. If one does not treat the mice used in the TVT Model with FVIII, all the mice die within 24 hours. When the parent molecules are given over 24 hours, 60 per cent to 70 per cent of the mice survive; this figures increases to 80 per cent if the FVIII is given 48 hours prior to the injury. Using PEGylated liposomes increases this survival rate to 80 per cent to 90 per cent.

Site-specific PEGylation allows a single PEG to attach to each of the FVIII molecules. A number of products, including FIX and FVIIa are making their way through pre-clinical trials. Longer-acting coagulation molecules are being developed, deimmunized coagulation proteins are proving challenging, and small molecule peptides and nucleic acid-based FVIII and FIX replacement therapies are proving very challenging, as are oral, pulmonary, and subcutaneous delivery. Dr. Pierce concluded that work would continue on universal procoagulants and gene transfer.

Research toward a longer-acting FVIII

Bruce M. Ewenstein, Baxter US

With an ample supply of pathogen-safe product, the focus can now move to therapeutic convenience and improvements, and a cure, said Bruce Ewenstein.

Great progress has been made in understanding how FVIII works at the molecular level. We know that the process involves Heparan sulphate proteoglycans (HSPGs), a low-density lipoprotein-related receptor (LRP) or an LDL receptor, and a complex interaction of these molecules with both FVIII and VWF. The goal is to block the clearance mechanisms to improve its half-life. Two broad approaches can be taken: direct modification and indirect modification. In the former, one can imagine FVIII mutants that are resistant to clearance, inactivation, or degradation. It may be possible to have biochemical modification of the FVIII such as with PEGylation or glycosylation. In the indirect approach, one can imagine interfering with receptor mediated clearance with FVIII or developing formulations with improved stability. However, these receptors are quite promiscuous, said Dr. Ewenstein. Interfering with them can result in a much broader effect. Another approach is to modify the VWF, which serves as the FVIII carrier protein. Baxter is using four approaches for half-life extension of FVIII, pursuing both direct biochemical modification of FVIII and indirect biochemical modification of VWF with two approaches: PEGylation and glycosylation modification.

PEGylation will enhance the solubility of proteins, decrease the proteolysis, alter distribution and absorption, enhance storage stability, and increase the half-life. Most drugs developed to date, however, are relatively small proteins or peptides. The primary mechanism has been to interfere with renal clearance. The effect of PEGylation on these much larger proteins such as VWF is not known, nor is the effect of long-term exposure or their impact on immunogenicity.

Experiments have confirmed that PEGylated rFVIII lasts approximately twice as long in FVIII-deficit mice than rFVIII does, which provides encouragement that such an approach is scientifically feasible. FVIII–VWF complexes will prevent FVIII from interacting with

lower affinity binding partners, such as LRP. There is a good correlation between pre-infusion levels of VWF and the half-life of FVIII in severe hemophilia A. It is therefore extremely reasonable to think that modifying the VWF will secondarily affect the plasma levels of FVIII.

Early demonstration shows that it is possible to successfully PEGylate rVWF. This is the largest protein that has ever been successfully PEGylated. Experiments in mice have shown that the half-life of rVWF improves dramatically with PEGylation. As hoped, modifying the VWF has a significant impact on the FVIII in the circulation, said Dr. Ewenstein.

Baxter is pursuing a parallel approach to this research using Polysialic Acid (PSA) technology as an alternative to PEGylation. PSA is both non-immunogenic and degradable to a much greater extent than PEGs, so this approach deserves a second look. Mouse experiments have shown that polysialylation successfully prolonged the half-life of VWF and sustained the secondary rise of FVIII. This remains "very much on the table as a clinical development program," said Dr. Ewenstein.

Discussing the impact of prolonged half-life from a clinical perspective, Dr. Ewenstein said that one of the paradigms of hemophilia treatment is that keeping the levels of FVIII at 1 per cent would significantly reduce the amount of bleeding. Although earlier research using a linear regression model had suggested only a weak association between the FVIII level and the annualized bleeding rate, more recent research using a negative binomial distribution found an extremely close fit. In other words, it confirmed a high correlation between the time under 1 per cent and the amount of bleeding. For each additional hour in the week that FVIII is below 1 per cent, there is a 2 per cent increase in the annual rate of hemarthroses. There is a significant effect to being over 1 per cent: if it were possible to always be above 1 per cent, the probability of avoiding a joint bleed would be 60 per cent. If it were possible to keep patients above 1 per cent, they could expect better quality of life and better outcome.

No one will accept an increase in immunogenicity as the cost of an increased half-life, commented Dr. Ewenstein. Experiments provide reason to believe that PEGylation will not raise immunogenicity. With increased dosages, PEGylated FVIII shows far less of an immune response than for the native rFVIII.

Noting that there are different levels of care globally, Dr. Ewenstein said that it is his hope that the process and speed of introducing new products globally would improve.

Patient perspective

Yuri Zhulyov, President, Russian Hemophilia Society

Speaking personally, Yuri Zhulyov noted that he has participated in a clinical trial. Of course he does not know which product he is being given, but so far, cannot feel any difference with the exception of a longer period between bleedings. He has experienced no negative effects.

Mr. Zhulyov stated that like all people with hemophilia, he looks forward to the development of new products that will reduce the number and frequency of injections, and thus allow patients more freedom.

Because Russia is such a large country, a reduction in the amount of product needed means that it will be easier to deliver. Increasing the prophylactic effects of a product will allow help to reach more people, said Mr. Zhulyov. Finally, cost is very important in Russia, as is informational support.

Discussion

A participant commented that rather than focusing on half-life, a better approach would be to target the place of injury.

Tongpil Min from the National Research Council of Canada said that although it is important to increase the half-life of the product, he was concerned about how this product would react in a surgical context.

Dr. Pierce replied that before surgery is contemplated with these longer-acting products, one would have to know that they work as well at time zero as the parent molecule. Dr. Ewenstein added that it is possible that some of these longer-acting FVIII molecules would be used for prophylaxis. At times of surgery one could possibly return to the earlier products to obtain peak responses, much like one uses short-term and long-term insulin.

Dr. Min also asked about allergic reaction. Dr. Ewenstein noted that these new products are not yet in clinical trial. If these molecules show large amounts of hypersensitivity, it could end their clinical trials.

Dr. Farrugia asked Dr. Pierce why he had been mute about the different routes of administration. Is there any interest in, for example, liquid formulation? Dr. Pierce replied that considerable work had been done in the 1990s on subcutaneous administration for FVIII and FIX, with little success. It took 20 years to bring inhaled insulin—with a molecular weight of 5,000—to market. FVIII has a molecular weight of 270,000–280,000, so it will not be likely get through to the lungs as an inhaled product. Dr. Ewenstein agreed.

Dr. Ruiz asked if the researchers had any data on immunogenicity of PEGylated FVIII molecules. Dr. Pierce replied that the clinical work done to date is not showing any immunogenicity when delivered via liposome. However, it will be necessary to wait until there is data for humans before gaining a better understanding. Dr. Ewenstein suggested that developing new animal models for immunogenicity would be an important step that would allow researchers to screen for this problem in pre-clinical trials.

Gene therapy in hemophilia

This session also started with a poll.

Question 14

Will gene therapy for hemophilia be available to patients?

Yes, in 5 years	4%
Yes, in 10 years	20%
Yes, in 15 years	61%
Never	15%

Curing bleeding disorders: Gene therapy—a means to the end?

Glenn Pierce, Founding co-chair of the NHF Gene Therapy Workshops

Commenting that he was speaking as a volunteer, Dr. Pierce described the NHF Gene Therapy Workshops over the last 15 years.

First he provided a retrospective. The biotech industry was born in the mid-1970s. Gene transfer experiments in dogs have been successful in curing hemophilia, but have not proven reproducible in humans. Genes for FVIII and FIX were cloned in the early 1980s, helping to establish the concept of gene therapy. The first immunodeficiency disease trials were initiated in 1989 and the first NHF-NIH collaborative workshop was organized in 1992.

Recalling an article he had published in the Summer 1990 edition of Hemalog, "A Cure by the Year 2000: Will the prediction come true?" Dr. Pierce said that the question is interesting, not so much for its ability to predict the future, but by the way in which this goal became a catalyst for focusing research, advocacy, education, and fundraising. To further these goals, Dr. Pierce and colleagues organized gene therapy workshops beginning in 1996. Eight have been held to date bringing together participants from industry, academia, government, and the hemophilia community.

Animal models have been very important in hemophilia research, noted Dr. Pierce. The dog and the mouse models have provided a tremendous amount of information—all current products in hemophilia therapy have been tested on dog models. These animals have seen lifelong cures beginning in the 1990s. At the same time, the NHF Medical and Scientific Advisory Council has been active in monitoring this field, advocating for responsible research for clinical trials, and promoting the ethics and responsibilities that accompany gene transfer.

Gene therapy clinical trials in the United States have involved 41 subjects to date, using a variety of vector systems. For the most part, the trials were safe and effective, but they did not produce the hoped-for cure. Dr. Pierce mused if this was a case of "one step forward, two steps back." A patient death attributed to adenoviral therapy (not for hemophilia) in 1999 had an enormous impact on this research as did the subsequent deaths of a child from leukemia following his cure (from SCID) by gene therapy. In contrast to the lifelong cures for multiple diseases (both genetic and acquired) effected in dogs, little efficacy was

detected in humans. On the other hand, the field has developed significantly. In all, over 30 patients have been treated and cured. Three have since developed leukemia: one died and two are in remission. However, all would now be dead without the gene therapy. Dr. Pierce suggested the science could be approaching the "two steps forward, one step back" stage.

It has become clear over the past 15 years that not all vector systems are alike. The preferred system for delivering FVIII or FIX into cells is viruses, which account for much of the toxicity. The interactions between host defences and the virus, and the processes involved in getting the DNA into the nucleus are complicated and not well understood.

Research into AAV-mediated gene transfer for hemophilia B with 15 patients showed some evidence of gene transfer but the patients had insufficient circulating FIX for a cure. Liver delivery, rather than muscle delivery, showed better circulating levels that would cure the disease but they were not sustained over the long term in humans because of limitations imposed by the host immune response.

Although the science has moved forward over the intervening years since the first workshop, the priorities and issues have changed little. Of the 400,000 people with hemophilia worldwide, only 100,000 receive some form of treatment. Many children die undiagnosed, especially in countries with a low GDP.

Gene therapy as a means of effecting a cure will be very expensive. Well over US$500 million has been invested to date. Other solutions for funding may include the model for developing vaccines or academic-industry/government-NGO collaborations.

The next steps for gene therapy include new research hypotheses, new DNA delivery vectors, designer molecules, and means of evading host immunity. Since the discovery of DNA in the 1950s, the focus of hemophilia has progressed from symptomatic treatment to regular prophylaxis to reduced infusion frequency to a cure. However, stated Dr. Pierce in closing, "If we don't think about this globally and treat those who currently have no access to protein-based replacement therapies, how will they benefit from gene therapy?"

Gene therapy update

David Lillicrap, Professor, Department of Pathology and Molecular Medicine, Queen's University, Kingston, Canada

David Lillicrap noted that hemophilia gene research has been a work in progress for the past 25 years. Six clinical trials have taken place involving 43 patients: three trials using FVIII gene transfer and three using FIX gene transfer. Outcomes show that gene transfer works in humans, albeit in lower levels and maximally for several days to weeks, with no significant adverse effects. Hemophilia is the ideal candidate disease for gene therapy; Dr. Lillicrap said that he is optimistic it will work within the next decade.

Dr. Lillicrap showed two slides depicting Avigen Patient E results. The adeno-associated virus vector serotype 2 (AAV-2) delivered human FIX gene, which was regulated by a liver-specific enhancer and promoter that expressed the transgene in the liver after delivery by hepatic artery injection. Two weeks after delivery of the vector, the FIX levels peaked at 12 per cent and remained therapeutic (above 1 per cent) for two months before becoming undetectable. Coincident with the falling FIX levels, the ALT and AST levels peaked at about 600 units, showing a cytotoxic response. These results had been well predicted by results from the Chapel Hill dog studies.

A subsequent patient treated on this trial showed increases in ALT and AST, which coincided with an expansion of AAV capsid-specific CD8+ T cells. It appears as though these hepatocytes were dying and releasing their enzymes because they were being attacked by memory T cells that had accumulated in the patient due to prior exposure to the AAV virus.

Translating the animal success with AAV—which at this point is the best candidate for delivering genes effectively—is problematic because as many as 80 per cent of humans have seen this virus previously. Researchers will have to circumvent these immunological issues.

AAV has been in the news recently. In a gene transfer trial, 127 patients with severe inflammatory arthritis had a soluble TNF receptor that uses AAV as the vector injected into their joints. One patient—a 36-year-old woman with a 15-year history of rheumatoid arthritis—died in July. Autopsy results show that she had disseminated histoplasmosis and HSV, and attribute her death to a retroperitoneal hematoma that may have been from a burst mycotic aneurism. A recent review of this case by the National Institutes of Health Recombinant DNA Advisory Committee discussed issues of informed consent and conflict of interest, and had very positive comments about the hemophilia community's efforts to educate patients about gene therapy. The role of gene therapy in this particular patient's death is not clear. Vector-related pathology may have contributed in a small way but was certainly not a direct cause. The multiple levels of immunosuppressant this patient was receiving probably contributed in a major way to the fungal disease that killed her.

While one type of AAV integrates regularly into the genome, the recombinant form of the virus does so very infrequently. A recent study (Sands et al., Science, July 2007) showed that in a lysosomal storage disease mouse model, one-third of the mice followed out beyond one year developed hepatocellular cancer. If those mice were treated with marrow transplantation (i.e., not with gene transfer), there was a background development of cancer of about 4 per cent. This raised the spectre of insertional mutagenesis with this virus. This study has generated considerable discussion and controversy. Dr. Lillicrap stressed that the majority of research has found no evidence of AAV-mediated tumorigenesis after long-term follow-up in pre-clinical studies. The community suspects a problem with this mouse model.

Two planned hemophilia FIX gene transfer therapy trials are set to begin within the next year. One will use hepatic artery injection with the same promoter construct and four months of T cell immunosuppression to try to remove the CD8+ response that many think is responsible for the cytolytic response seen earlier. The second study involves using a self-complementary serotype AAV-8 and a systemic injection. Immunosuppression will only be used as a second-line therapy in the event of problems.

Other approaches include using other AAV serotypes, systemic delivery with other viruses such as lentivirus, ex vivo delivery with genetically modified autologous adult stem cells, and targeted integration strategies to avoid insertional mutagenesis. These are very complicated issues that will probably not see results within the next five years. Continuing challenges include host immune response to both the vector and transgene product, achieving persistent therapeutic levels of transgene expression, and insertional mutagenesis.

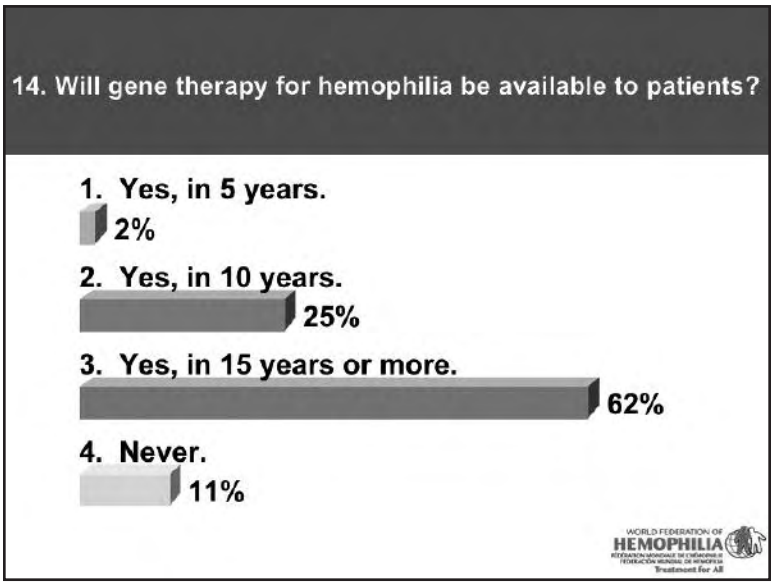
Dr. Lillicrap pointed out that the first commercial gene therapy product, Gendicine, was licensed in China two years ago and is being used extensively in cancer-related gene transfer therapy. Although many think of these gene therapies as being confined to the developed world, it is important to understand that this kind of technology is being developed around the world.

Discussion

David Page repeated the previous question:

Question 14 (repeated)
Will gene therapy for hemophilia be available to patients?

Yes, in 5 years	2% (4% first time)
Yes, in 10 years	25% (20% first time)
Yes, in 15 years	62% (61% first time)
Never	11% (15% first time)



Powerpoint slide from WFH Fifth Global Forum on the safety and supply of treatment products for bleeding disorders

Sol Ruiz commented that participants at the last meeting of the gene therapy working party at the EMEA came to the same conclusion about the death of the 36-year-old woman in the inflammatory arthritis AAV trials. The group has seen the same adverse events with the treatment of therapeutic protein products such as Humira, Embrel, and Remicade in immunosuppressing patients, and concluded that the gene therapy did not play a role in the death.

Dr. Ruiz asked the panel members if they thought there would be a problem—similar to the one with therapeutic proteins—with inhibitors if they were able to achieve a long-term expression.

Dr. Lillicrap replied that the paradox with gene therapy is that on one hand, the possibility of inciting new inhibitors must always be kept in mind. Depending on how one delivers the transgene, the risk can be minimized or accentuated. Delivering with an immunogenic virus such as adenovirus increases the likelihood of getting inhibitors. Other ways of delivering the transgene would minimize that risk. On the other hand, gene therapy can be thought of as alternative way of delivery prophylaxis in long-term constant levels. Using gene transfer as a tolerizing strategy holds considerable promise.

Tongpil Min asked if increasing the rate of survival of the vector might increase the rate of leukemia development. Dr. Pierce replied that he doubted there would be a risk of leukemia from using AAV vectors. They contain no genes from the original virus. The leukemia was only in a particular kind of mouse that had lysosomal storage disease deficiency in which the liver is destroyed by the disease process. This is an artificial situation that has not been seen in any of the hemophilia mouse models, the dog models, or any of the other mouse models used.

Dr. Lillicrap said that it is important to remember that the transgene product being delivered was a growth factor receptor, which gave the cells that were transduced a proliferative advantage. There is no reason to believe that FVIII or FIX cells would provide a cellular advantage when expressed. This product being delivered is benign in terms of oncogenesis. The product being delivered to the SCID children clearly set up a growth advantage for those cells, which was one of the components that initiated the leukemogenesis. Dr. Pierce added that all vector systems are not alike. These SCID children had been given a vector that deliberately inserts into the host genome, which is not the case with AAV.

Ed Gomperts mentioned that the SCID model with a different vector is moving ahead very positively. Researchers are almost on the cusp of having a preferred therapy for this rare disease. He mused about whether it would be possible to apply this technology to hemophilia therapy by modifying it with the lentivirus vector. This way one could avoid the AAV vector that is proving to be problematic. Dr. Lillicrap agreed that no one knows the eventual winner, so using different strategies makes sense. Using adult stem cells is showing good pre-clinical results.

Marijke van den Berg asked if it is possible to screen patients to determine if they are negative for previous AAV exposure. Dr. Lillicrap responded that theoretically, this is possible. However, the bad outcome in the patients described was due to cellular immunity. The primed memory T cells are sequestered in parts of the body that one cannot access. There is not a good correlation between seropositivity and the presence of these memory T cells. “It’s a great idea,” he concluded, “but unfortunately it’s not easy to do.”

Dr. Pierce added that the majority of people are exposed to AAV as children.

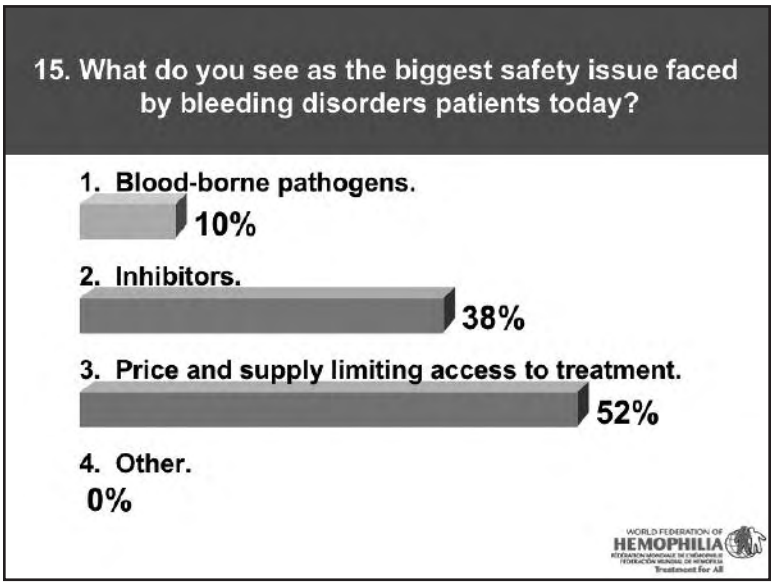
Emerging and ongoing safety and supply issues update

Session chair David Page polled participants.

Question 15

What do you think is the biggest issue faced by bleeding disorders patients today?

Blood-borne pathogens	10%
Inhibitors	38%
Price and supply limiting access to treatment	52%
Other	0%



Powerpoint slide from WFH Fifth Global Forum on the safety and supply of treatment products for bleeding disorders

Safety issues for factor concentrates update: 2007

Albert Farrugia, WFH Blood Safety Advisor

Albert Farrugia commended participants for expressing, through their voting, that blood-borne pathogens and safety issues are not a thing of the past, but are no longer the major focus of concern. He highlighted several developments that had arisen since the last Global Forum, particularly stressing a number of issues arising out of the US Federal Drug Administration (FDA) review of vCJD risk from UK-sourced plama products.

Like all regulatory agencies that have done similar reviews in the past, Dr. Farrugia said, the FDA created a mathematical model, which showed that people with hemophilia exposed to factor concentrates are at the highest level of risk of all blood recipients, even though that risk is quite small. The quantitative inputs for the model are still the subject

of debate, the inputs chosen affect the output. One of the most important inputs is the prevalence of vCJD in the UK population. There is still serious disagreement about whether to accept prevalence data based on tonsillectomy and other surgical procedures or more optimistic data.

A model, developed by Steve Anderson, examines various parameters influencing final risk output and assesses the impacts of a number of components:

- Log manufacture reduction of vCJD agent
- FVIII used per year
- Number of cases of vCJD in UK
- Efficiency of route of infection
- Quantity of infectivity in blood
- FVIII yield from plasma
- Effectiveness of donor deferral policies

Dr. Farrugia said this model shows that the biggest positive impact on safety comes from the log reduction achieved in the manufacturing process, while donor deferral programs have a much more moderate effect.

He also presented a brief overview of two prion filters, both of which are in the late stages of development. The first of these is an updated version of the existing leukocyte filters and has been demonstrated to successfully remove endogenous infectivity from blood. The P-Capt™ filter from MacoPharma pulls the agents out of either red-cell solutions or plasma. It has effectively filtered prions out up to the maximum sensitivity levels of the assays.

Several new tests were described at last year's Transmissible Spongiform Encephalopathies (TSE) Advisory Meeting, Dr. Farrugia said. The first is Protein Misfolding Cyclic Amplification (PMCA), which is somewhat analogous to NAT testing and appears to be capable of detecting pathological pre-disease development. Another test, developed by TSE Diagnostics, uses a straightforward Enzyme-Linked ImmunoSorbent Assay (ELISA) test. In sheep models, PMCA has detected material in the blood before the sheep get sick. Dr. Farrugia described both of these tests as indications that significant advance toward an effective and reliable screening test has taken place.

The methodology is also now available for hepatitis B NAT testing, he said, although the cost-effectiveness for this test has not yet been determined.

The most interesting emergent agent in the past year or two has been pandemic influenza, according to Dr. Farrugia. He reviewed several studies that suggest how to deal with blood supply in face of a pandemic. Fractionation and inactivation models developed for influenza indicate that this virus is inactivated by processes that already exist, such as vapour heating, solvent detergents, and pasteurization in albumin.

At this time, recipients of hemophilia concentrates can be relatively secure about the safety of products, Dr. Farrugia concluded. Although nature will continue to challenge us with new pathogens, the inactivation processes developed over the past 20 years should be capable of dealing with any possible new agents.

Blood-borne pathogen surveillance project

Bruce Ritchie, Division of Hematology, University of Alberta

Bruce Ritchie began by noting that surveillance is a "numbers game," and that rare adverse events will not be identified unless large numbers of patients are observed, which requires large multinational studies. For example, he noted, there are many studies about inhibitors, which he characterized as rare adverse events. However, there is still no agreement about whether there is a difference between inhibitor prevalence and the use of recombinant versus plasma-derived products. He asked participants to consider who had the reach to examine multiple products and whether WFH had a role to play in facilitating this large-scale multi-product surveillance.

He reviewed the story of Viox in Canada, noting that the drug was particularly important in the hemophilia community because of its work in treating arthropathy. He reminded participants that Vioxx was licensed by Merck in Canada in 1999 and was hailed as a revolutionary anti-arthritis drug. The original licensure, based on 5,000 patients, showed no increase in cardiovascular risk.

The CLASS and VIGOR studies, each of which had over 8,000 enrolled patients both demonstrated some cardiovascular risk, but it was deemed to be outweighed by gastrointestinal benefit, Dr. Ritchie said. However, the Adenomatous Polyp Prevention on Vioxx Study (APPROVe) of 2,600 patients found a four-fold cardiovascular risk. As a result, the product was voluntarily removed from the market in 2004. Unfortunately, despite the fact that Vioxx was the most effective anti-inflammatory drug for hemophilic arthropathy, and the increased platelet aggregation it caused may be beneficial in bleeding disorders, it is no longer available.

He said the Vioxx experience demonstrated what is often wrong with post-market surveillance. When the drug was withdrawn, it was removed from the whole community—not just those at high risk. The manufacturer is adamant that the drug will never again be available in Canada, despite the fact that it continues to be a useful drug in certain cases.

He likened the difficulties with post-market surveillance of Vioxx to studies to determine whether the prevalence of inhibitors is product related. Licensing studies for plasma-derived and recombinant FVIII products show a background inhibitor rate of 20 to 25 per cent in previously untreated patients (PUPs), with 10 to 15 per cent developing significant long-term inhibitors. Inhibitors are rare in previously treated patients, and no difference was found in their prevalence when using rFVIII.

However, studies conducted on two cohorts of French patients suggest that product choice is nearly as important as ethnicity for inhibitor risk. He said he would applaud manufacturers for conducting post-market surveillance, but that it was not enough. It is important to find ways to compare the use of these products over the long term in real world use.

Dr. Ritchie outlined several recent studies on inhibitor prevalence as it related to product choice. He asked who should actually be conducting post-marketing surveillance, noting that bleeding disorders are fairly rare, and the detection of rare events is even more difficult. Pharmaceutical companies monitor their own products, but no one appears to be monitoring the whole market. Studies must be conducted in a more standardized fashion. He questioned whether harmonization between regulators was sufficient and, again, raised the possibility that there could be a role for a global organization like WFH in driving global, whole market surveillance.

He noted that people often suggest that treatment products are safe because there has been no pathogen transmission. There have, however, been significant failures of viral detergents and transmissions of parvovirus in 1996 and hepatitis A in IVIG products. New and existing pathogens are always at risk of getting into the blood system, so it is imperative that adequate surveillance take place to detect them, and cope with them in a timely fashion. Vigilance is extremely important.

Dr. Ritchie briefly reviewed the hemophilia surveillance projects occurring in Canada, including the Canadian Hemophilia Registry, the Canadian Hemophilia Assessment and Resource Management System (CHARMS), and the Canadian Blood-borne Pathogen Surveillance Project, which is studying serial samples from patients with hemophilia A and B, VWD, and other rare bleeding disorders to look for known and emerging blood-borne pathogens and known and emerging genetic factors affecting the expression of underlying disease.

He reiterated that surveillance must be conducted in a more organized, systematic fashion and must examine all kinds of rare adverse events—not just pathogens and inhibitors. As gene therapy and transgenic treatments come on-line, it will be challenging to design rigorous studies and appropriate surveillance.

Discussion

Yuri Zhulyov, President of the Russian Hemophilia Society, asked for information regarding parvovirus and other small viruses, such as polio.

Dr. Farrugia said that parvovirus continues to be a challenge. Human parvovirus B19 is proving to be less resistant to inactivation than the animal viruses that had been used for early tests. However, it is still necessary to develop better assays. The behaviour of the polio virus toward inactivation has already been characterized and been found to be less resistant than B19.

Innovations

Treatments for rare bleeding disorders

Paula Bolton-Maggs, Consultant Haematologist, Manchester Comprehensive Care Haemophilia Centre, Manchester Royal Infirmary, Manchester, UK

The most important new development in treating rare bleeding disorders has been the increased global data collection regarding them, according to Paula Bolton-Maggs. This important information has created a foundation upon which manufacturers can be encouraged to develop treatment products.

The first WFH Global Survey was conducted in 1998, and it takes place annually ever since using a questionnaire that is sent to national hemophilia associations, who provide data in conjunction with physicians or health officials, Dr. Bolton-Maggs explained. The information is reviewed by a team at WFH, assessing the quality of data and issuing annual reports. Although the data quality differs from country to country, it is extremely valuable. Each year, data analysis "drills down" a little deeper.

In 2005, a new series of questions relating to rare bleeding disorders was introduced, she said. Using the information collected over time, it is apparent that the number of people diagnosed with VWD and hemophilia A and B has increased. Interestingly, though, the number of cases of rare or other bleeding disorders has increased by over 70 per cent between 2004 and 2006 to around 20,000, with over 87 per cent of the global population surveyed.

It is clear from the data that there are some inconsistencies in the information provided, Dr. Bolton-Maggs said. Some countries are clearly only reporting severe cases, while others, which possess more sophisticated diagnostics, are including milder ones. The biggest blocs of information are coming from Europe and North America, while only a small number of countries from Southeast Asia are reporting.

The commonest reported rare disorder is FVII deficiency with 1 reported case per 500,000 people. The least common is prothrombin deficiency with a reported incidence of 1 in 2,000,000. The distribution of rare bleeding disorders also differs in different parts of the world, Dr. Bolton-Maggs said. In Southeast Asia, the most common disorder is Glanzmann thrombasthenia (GT), which accounts for nearly half of all rare bleeding disorders reported. In the US and Europe, the incidence of GT is much lower, at 1 and 7 per cent respectively.

One of the biggest problems is FV deficiency because there is no concentrate available so treatment depends on virally treated fresh frozen plasma (FFP). The data and literature regarding FV deficiency is very limited, she said, and the consequences of the disorder can be severe.

There are a number of unlicensed virally inactivated concentrates for treating fibrinogen deficiencies. While cryoprecipitate is a good source of fibrinogen, it is not virally inactivated so it is not safe.

Treatments for prothrombin (FII) deficiencies exist in combination with other concentrates. However, it is unclear what happens when patients are loaded with other factors that are already sufficient in their systems.

Dr. Bolton-Maggs explained that rFVII is the treatment of choice for FVII deficiency, and some other combination concentrates are also available. There are currently no FX concentrates, so the most common treatments are intermediate purity FIX concentrates, which carry an increased risk of thrombosis, and FFP.

There are also several treatment options for FXI deficiency, including two concentrates, viral-treated FFP, and fibrinolytic inhibitors. FXIII deficiencies can be treated using a pasteurized plasma-derived concentrate, she said, noting that platelets also contain FXIII and can be useful in emergencies.

There is some good news regarding the development of new treatments for rare bleeding disorders, Dr. Bolton-Maggs said, although information is being very closely guarded at this point. The following products are in development: rFXIII, pdFV and rFV, plasminogen concentrate for ligneous conjunctivitis, rVWF, and ADAMTS13. Manufacturers are also seeking further evidence about the pharmacokinetics of rare bleeding disorders.

Preparation of solvent-detergent-treated mini pool blood products

Magdy El Ekiaby, Shabrawishi Hospital, Blood Bank, Giza, Egypt

Magdy El Ekiaby presented an overview of a program, which has been developed over the past four years, to prepare virally inactivated, solvent-detergent-treated cryoprecipitate, cryo-poor plasma, and plasma for use by blood establishments in Egypt.

The project's aim is to use reliable and affordable technology that can be implemented by blood establishments with minimum infrastructure investments, Dr. El Ekiaby said. The development and adaptation of solvent-detergent virus inactivation procedures into blood establishments will be enhanced by quality control and quality assurance measures to ensure effective and uniform plasma and plasma-derived products.

Before choosing appropriate production processes, he said, all technological options were evaluated. Viral detergent was chosen because it is a robust technology and there is less risk for transmission of non-enveloped viruses due to the size of the mini-pool.

The process involves a viral inactivation step, followed by solvent-detergent removal, then a chromatography absorption step, Dr. El Ekiaby explained. The process is conducted in a closed, disposable sterile processing system with equipment routinely used in blood establishments. Required equipment was limited to a laminar air flow cabinet, syringe pump, shaker, and shaker incubator to allow for the controlled and reproducible mixing of solvent-detergent agents. Reagents used are TnBP, Triton X45, soya bean oil, and +/- C18/SDR.

He outlined the process, which uses a patented interconnected closed sterile bag system for mixing the solvent detergent with plasma, and for extracting the solvent detergent. This single technology can be used for FFP, cryo, and cryo-poor plasma. Because the technique is very "gentle," it has no significant impact on the proteins and the level of factor recovery is very high. There was also no significant impact on VSF:Ag, VWF:Rco, VWF:CB, or VWF multimers. Residual TnBP was less than 10 ppm, and Triton X-45 less than 100 ppm.

Dr. El Ekiaby explained that this technology pools 40 units of cryo in one disposable bag, and yields 400 units in about six hours. The products can be used to treat hemophilia A and B, VWD, fibrinogen deficiencies, and severe postpartum bleeds. Future innovations may allow for mini-pool preparations of PCC, FIX, FVII, FXI, and FV.

Transgenic rFVIIa

Yann Echelard, Senior Director of Embryology, GTC Biotherapeutics

Sami Chtourou, Director, Biopharmaceutical Development LFB, Lille, France

Transgenic Production

Yann Echelard explained that transgenic animals carry heterologous DNA stably integrated into their genomes. Transgenic dairy animals can be used as "bioreactors" to produce recombinant proteins. The mammary gland is a prodigious protein production device, he said. Even a small incremental production increase can yield 5 to 10 grams per litre of protein, in concentrations 100 to 1000 times higher than in tissue cultures.

Dr. Echelard said the process does not harm the animals.

The technique involves linking a milk-specific promoter to a gene of interest, introducing the DNA into a single-cell embryon by microinjection or nuclear transfer. The transgenic animals that are generated express the target proteins in their mammary glands. The adult animals are milked and the recombinant protein is purified from the milk.

Because of the link between animal size, maturity time, and the amount of milk produced, goats, cows, pigs, and even rabbits are ideal, he explained. Once milk has been obtained caseins, fat, and other components must be filtered out. The typical yield is 40 to 50 per cent of the target protein with 99 per cent purity. Because of their relatively high milk production and short gestation periods, rabbits also make excellent transgenic animals.

The GTC farm in Massachusetts produces an annual output of 9-14 tons of milk much less expensively than a laboratory would, Dr. Echelard said. Over 150 proteins have been expressed in transgenic animals, including Alpha-1 Antitrypsin, antithrombin, LA-tPA, tPA, human albumin, Alpha-fetoprotein, prothrombin, TFPI, FX, and FVII.

Dr. Echelard described a GTC-LFB joint venture based on their mutual interest in recombinant plasma proteins and monoclonal antibodies, and complementary skill sets regarding research, development, manufacturing, and commercialization.

New rhFVIIa produced in transgenic milk

The advantages of using the milk of transgenic animals to produce biotherapuetic proteins is clear, Sam Chtourou said. Because of their experience in producing pdFVII and pdFVIIa, and the relatively monopolistic position of NovoSeven in the market, LFB decided to embark on its new rhFVIIa project. Another factor influencing their decision was the sustained increase in the use of FVII since 1999 and projected future demand increases. If forecasts are correct, by 2012 the demand for FVII will be double what it is today.

Dr. Chtourou said the project's goal is to provide an abundant, cost-effective, safe source of FVIIa for human therapeutic use by producing recombinant human coagulation FVIIa (rhFVIIa) in the milk of transgenic animals.

RhFVIIa will be indicated for patients with inhibitor levels greater than five Bethesda Units (BU), patients with congenital hemophilia who are expected to have a high anamnestic response to FVIII or FIX administration, and patients with acquired hemophilia.

Dr. Chtourou outlined several of the technical challenges the project faces:

- The need to obtain high expression and secretion of FVII in the transgenic animals' milk
- The development of a high-yield purification process
- The arrival at a product with the same purity, structural characteristics, functional properties, in vivo efficacy, and tolerance as recombinant or plasma-derived FVIIa

To date, the project has produced transgenic rabbits that produce human FVII in their milk, developed a process for the purification of human FVII from rabbit milk, and extensively characterized rhFVIIa in comparison to pdFVIIa and NovoSeven. From the results of different FVII assays, he said, rhFVIIa has proven to be functionally and biochemically comparable. Current work is focusing on optimizing yields, expanding transgenic herds, generating clinical and pre-clinical batches, and regulatory and clinical trial planning. In conclusion, Dr. Chtourou said, the cost-effective production of safe human FVIIa from transgenic animal milk is feasible.

Factor IX innovation

Edward Gomperts, Medical Director, Inspiration Biopharmaceuticals

Edward Gomperts explained that Inspiration Biopharmaceuticals is a company founded by the parents of two boys with hemophilia B, whose goal is to "revolutionize hemophilia treatment" by making treatment more economical, treating more patients, and allowing more patients access to prophylactic care if they choose it. Their longer-term goals are to use rFIX and existing technology as the platform for creating "next generation" rFIX and other Vitamin K proteins, such as FVIIa. They also aim to eliminate the need for needles, which would essentially cure the disease, he said.

There has been significant progress in the development of rFIX, Dr. Gomperts said. A proprietary rFIX cell line has been developed. Purification and formulation processes have been created, and successful commercial scale runs completed. Safety studies are in progress and the product for clinical trials has been produced.

The technology results in a significant increase in functional FIX expression, he explained. When product characterization is examined, there are significant similarities between the Inspiration protein and Mononine® and Benefix®, although the clinical recovery half-life in patients has yet to be determined.

Dr. Gomperts reviewed pharmacokinetic study comparisons in hemophilic dogs. He noted the two dogs were exposed to human FIX, developed inhibitory antibodies, then were tolerized. Their antigen and activity profiles were closely parallel.

The clinical trial protocol has been completed, he said. It includes three separate pharmacokinetic crossover evaluations. The initial pharmacokinetic crossover will include an evaluation of thrombogenicity. Patients will choose on-demand or prophylactic treatment, which will be evaluated for efficacy, inhibitor risk, and safety. There will be a follow-up evaluation of pilot product versus that produced at the commercial facility once it comes on-line, and a separate pharmacokinetic evaluation of the Inspiration product versus Mononine.

Surgical efficacy and safety will be assessed, he added, noting that continued evaluation of safety and efficacy would take place through potential licensure and the continuation phase. All of these studies will be multinational.

Discussion

Brian O'Mahony asked if Dr. Gomperts expected a recovery broadly similar to Benefix. Dr. Gomperts said there had also been similarity with plasma-derived products. Although, recovery is still unknown, he said he expects the Inspiration product will more closely resemble Benefix based on dog trials.

Closing summary and discussion

Mark Skinner thanked all the speakers, commenting that it had been a fascinating conference that covered a wide range of topics. The issues discussed were issues of the future: what the community will need to achieve the WFH vision of Treatment for All.

The opening session discussed Quality of Life instruments. So much of what is done when evaluating how countries are progressing centres on how much factor the country is using. Treatment for All means so much more than factor, stressed Mr. Skinner. It will be important to develop a global Quality of Life instrument. The information that comes from that can be quite useful as the WFH develops other aspects of its hemophilia care program that are not clotting factor dependent.

"Our survey results show that inhibitors are very much on people's minds," noted Mr. Skinner. "It is quite exciting to see that the blood-borne pathogens are moving down on that list." At this point there are more questions than answers about inhibitors. The challenge will be how to put this in perspective for the patients, or put it in context with the other risks that patients who chose alternative treatments might face. Progress on global collaboration is being made.

In the economic sessions, Mr. Skinner said that he was intrigued by the audience perceptions of the most important economic considerations. At the end of the session the general audience recognized the importance of research and development as cost drivers, but when only those purchasing the factor were polled, they showed a very different expectation of the cost drivers for their country. This disconnect is not easily resolved, but it does highlight the need to ensure that pricing allows research and development to occur, and the need for education.

Biosimilars and gene therapy both show hope and promise for the future. The results may not be realized for five or ten more years, but progress is evident on all fronts. Biosimilars or the longer lasting half-life products may be realized first. "The future is quite bright for the hemophilia community and each innovation will make a big difference as we try to bring treatment to other regions of the world," said Mr. Skinner.

Mr. Skinner thanked all the companies that put time and effort into supporting this forum and advancing hemophilia care.

He then concluded the session by asking three questions.

Question 16

What is the most important consideration in selecting a treatment product?

Price:	9%
Inhibitor risk:	37%
Pathogen risk:	21%
Efficacy:	33%

Powerpoint slide from WFH Fifth Global Forum on the safety and supply of treatment products for bleeding disorders

Question 17

Did the Fifth WFH Global Forum on the Safety and Supply of Treatment Products for Bleeding Disorders meet your expectations?

Exceeded expectations:	34%
Meet expectations:	62%
Not meet expectations:	4%

Question 18

Where would you like the next Global Forum to be?

Montreal:	38%
North America, but not Montreal:	7%
Europe:	48%
None of the above:	7%

A participant asked if the survey question about important considerations could be repeated without industry participation. The results are below:

Question 16 repeated

What is the most important consideration in selecting a treatment product?

Price:	7%	(compared with 9%)
Inhibitor risk:	38%	(compared with 37%)
Pathogen risk:	22%	(compared with 21%)
Efficacy:	33%	(the same)

Mr. Skinner once again thanked participants for coming, commenting that he appreciated their concern and support.

Acronyms

AAV:	adeno-associated virus
AAV-2:	adeno-associated virus vector serotype 2
APPROVe:	Adenomatous Polyp Prevention on Vioxx (Study)
aRR:	adjusted relative risk
BU:	Bethesda units
CBER:	Center for Biologics Evaluation and Research
CDC:	Centers for Disease Control and Prevention
CEDs:	cumulative exposure days
CFC:	clotting factor concentrate
CHARMS:	Canadian Hemophilia Assessment and Resource Management System
COCHE:	Cost Of Care of Hemophilia Study
COCIS:	Cost Of Care Inhibitors Study
ELISA:	enzyme-linked immunosorbent assay
EMEA:	European Agency for the Evaluation of Medicinal Products (also called European Medicines Agency)
ESCHQoL:	European Study of Clinical, Health economic and Quality of Life outcomes in Haemophilia treatment
FDA:	Food and Drug Administration (US)
FD&C:	Food, Drug, and Cosmetic (Act) (US)
FFP:	fresh frozen plasma
FII:	factor II (prothrombin)
FIX:	factor IX
FV:	factor V
FVII:	factor VII
FVIIa:	activated factor VII
FVIII:	factor VIII
FX:	factor X
FXI:	factor XI
FXIII:	factor XIII
GAP:	Global Alliance for Progress (WFH)
GDP:	gross domestic product
GMP:	good manufacturing practice
GT:	Glanzmann thrombasthenia
GTH:	German, Austrian, and the Swiss Society of Thrombosis and Hemostasis Research
HCP:	host cell proteins
HSPGs:	heparan sulphate proteoglycans
ICH:	International Conference on Harmonization

Acronyms

ISTH: International Society of Thrombosis and Haemostasis
ITI: immune tolerance induction
IVIG: intravenous immunoglobulin
LRP: low-density lipoprotein-related receptor
MTP: minimally treated patient
NAT: nucleic acid testing
NGO: non-governmental organization
NHF: National Hemophilia Foundation (US)
NHFT: National Hemophilia Federation of Thailand
NHS: National Health Service (UK)
NHSO: National Health Security Office (Thailand)
NMO: national member organization (WFH)
PCC: prothrombin complex concentrate
PD: plasma-derived
pdFV: plasma-derived factor V
pdFVIII: plasma-derived factor VIII
PHS: Public Health Service (US)
PMCA: protein misfolding cyclic amplification
PUP: previously untreated patient
QoL: quality of life
rFIX: recombinant factor IX
rFV: recombinant factor V
rFVIIa: recombinant factor VIIa
rFVIII: recombinant factor VIII
rVWF: recombinant von Willebrand factor
TCM: tail clip model
TSE: transmissible spongiform encephalopathies
TVT: tail vein transection
vCJD: variant Creutzfeldt-Jakob disease
VWF: von Willebrand factor
WFH: World Federation of Hemophilia

WORLD FEDERATION OF
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FEDERACIÓN MUNDIAL DE HEMOFILIA
Treatment for All

World Federation of Hemophilia

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