WFH
GLOBAL FORUM

on the Safety and Supply of Hemophilia Treatment Products

Montreal, Canada
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WFH Global Forum – Executive Summary

More than 100 participants from around the world gathered in Montreal for the second WFH Global Forum on the Safety and Supply of Hemophilia Treatment Products. The forum included representatives from major regulatory bodies, leading scientists, specialists, clinicians in the field, leaders from hemophilia societies, and representatives of commercial and not-for-profit producers of blood products.

Discussion focused on the two critical issues of variant Creutzfeldt-Jakob disease (vCJD) and the recombinant product shortage. As outbreaks of bovine spongiform encephalopathy (BSE) spread in Europe and now in Japan, and new cases of vCJD are being diagnosed, the bleeding disorders community is becoming very concerned with this threat. Issues addressed at the forum included: can vCJD be transmitted by blood? What is the level of risk? What measures are being taken to minimize risks? Has communication about vCJD been effective or alarmist?

The recent recombinant shortage, which began in March 2001, has become the primary concern for the community as patients are forced to switch products, treatment regimes are altered, and surgeries and other procedures are being postponed. Discussions focused on what the cause and effects of the shortage were, and how shortages can be avoided in the future.

Different points of view on various issues were presented, including those of industry, treaters, regulators, and patients. In his opening address, Brian O'Mahony, President of the World Federation of Hemophilia, said the goal of the meeting was not to change viewpoints, but to bring new perspectives into an open and constructive dialogue on the issues.

To encourage participation and give everyone a say in the discussion, each participant had an electronic voting pad to capture audience opinion on the issues. To determine the impact of the discussion on people's opinions, the same questions were asked at the beginning and end of a session. On some issues, different groups of participants (patients, regulators, industry, etc…) were asked to vote separately, which revealed some interesting differences.

Transmissibility of vCJD

One of the most important concerns for the hemophilia community is whether vCJD is transmissible by blood. Scientists, treaters, and other presenters shared the latest information with forum participants.

There is no epidemiological or experimental evidence of vCJD transmission through blood transfusion or use of plasma-derived products, explained Larisa Cervenakova (The American Red Cross Holland Laboratory). However, data she presented on her experiments with mice inoculated with blood components from vCJD-infected mice did show that the disease was transmissible by blood under laboratory conditions in some instances. Noting that these data were not conclusive, Dr. Cervenakova told the audience that she looked forward to additional data, which she hoped would help answer the question of whether or not blood from patients with vCJD is infectious.

Charles Waller (Plasma Protein Therapeutics Association, Europe) said there is no evidence that people with pre-clinical or clinical CJD, including vCJD, carry infectious prions in their blood or have transmitted infectious prions through any blood products. Despite the mounting evidence that vCJD is not transmissible through blood products, Mr. Waller stressed, the industry continues to treat the theoretical risk as a real risk.

Wolfgang Schramm (Ludwig-Maximilian University Hemophilia Centre) agreed, stating that the transmission of vCJD via plasma seems unlikely since the agent is almost completely eliminated during the production process. Although it is never possible to create complete safety, Prof. Schramm contended that the blood supply is the safest it has ever been. Still, from a treater's perspective, it is critical to balance safety measures with supply concerns, he said. Hemophilia is a life- and limb-threatening disease that necessitates that real risks must be balanced, and that includes the risks attendant upon product shortages, he said.

This subject generated much discussion and debate. A number of participants cautioned against being overly optimistic regarding the evidence on vCJD transmission so far. It is too soon to say, conclusively, that the results of real cases of vCJD patients are reassuring, another participant said, while stressing that theoretical studies have been much less reassuring.

There was a marked change in opinion of patients on whether vCJD can be transmitted through blood products. At the start of the session, 22 percent of respondents agreed that vCJD could be transmitted through blood products, but at end of the session, 43 percent agreed.

"With regard to the risk of transmission of vCJD via replacement therapy, are you very concerned, concerned or not concerned."

Beginning of session:

Very concerned:	11%
Concerned:	62%
Not concerned:	28%

End of session:

Very concerned:	13%
Concerned:	64%
Not concerned:	22%

"In the light of evidence currently available, do you believe that vCJD can be transmitted through the infusion of coagulation factor concentrates?"

Beginning of session:

Non-patients:	
Yes:	13%
No:	55%
Don't know:	33%
Patients:	
Yes:	22%
No:	28%
Don't know:	50%

End of session:

Non-patients:	
Yes:	13%
No:	55%
Don't know:	33%
Patients:	
Yes:	43%
No:	29%
Don't know:	35%

Other issues addressed the need to learn more about TSEs.

Ana Padilla (World Health Organization) described the WHO's activities on vCJD, including a project for the development of international reference materials for the diagnosis and study of human TSEs (both spCJD and vCJD). Considerable progress has been made in the development of laboratory tests for the detection of the pathological protein (PrP^{Sc}), she reported, but the predictive values of these assays in terms of TSE infectivity have not been independently confirmed.

During the open forum session, Glenn Pierce (National Hemophilia Foundation) noted that the link between prions and infectivity is unclear. Participants had wide-ranging opinions on whether prions caused vCJD. One likened doubting the link between prions and vCJD to governments claiming that they don't know what causes AIDS. Another suggested that although prions are the likely culprit, there is still a possibility that vCJD may be a virus.

Assessing and Minimizing Risk

Discussion about assessing and minimizing risk focused on techniques for evaluating risk in times of uncertainty and the difficulty, for regulators and others, of predicting future outcomes. "We are forced to live with the reality that we cannot make decisions that eliminate all risk for all patients," said Bruce Evatt (Centers for Disease Control and Prevention, and WFH Vice-President Developing World).

Risk Assessment

Dr. Evatt set the stage by providing an insightful comparison on risk assessment comparing CJD and vCJD with HIV at similar points in their respective crisis timelines. He also provided some encouraging working assumptions on the risk of vCJD. He noted that the peak of BSE in Europe is predicted to occur between 2002 and 2005, and that the highest risk of plasma donor infectivity is in the U.K., France, and possibly Japan. In addition, he reported that current methods for producing factor VIII are expected to clear three to six logs of infectivity and factor IX manufacturing methods should clear seven logs.

Overall, participants did not perceive vCJD to be as serious a threat as HIV. By the end of the session, 88 percent of those in the audience voted that they did not perceive vCJD to be as dangerous as HIV was in 1982.

Do you feel that vCJD poses the same threat to the hemophilia community as HIV did in 1982?

Beginning of session:

Yes:	7%
No:	82%
Don't know:	10%

End of session:

Yes	5%
No	88%
Don't know	7%

Judging the relative risk in the face of numerous unknowns is the difficult task regulators face, said Manfred Haase (European Agency for the Evaluation of Medicinal Products). Risk analysis is a scientific evaluation of the probability of occurrence and the magnitude and severity of the effect. In areas of uncertainty, he noted, there should be a balance between the need for clinical data to evaluate risks and the avoidance of delays in making available efficacious medicinal products to patients in medical need.

Francine Décary (Hema-Québec) elaborated on the process of making decisions

regarding risk, using the example of the Canadian province of Quebec as a case study. The recommendation on the precautionary principle of the Commission of Inquiry on the Blood System in Canada was the motor for decision-making. The recommendation calls for the principle of safety to transcend other principles and it also states, "The balancing of the risks and benefits of taking action should be dependent not only on the likelihood of the risk materializing but also on the severity of the effect if the risk does materialize, on the number of persons who could be affected, and on the ease of implementing protective or preventive measures. The more severe the potential effect, the lower the threshold should be for taking action."

When asked to weigh the relative risk of vCJD versus shortages of factor concentrates, ***95 percent of participants, and 91 percent of patient group representatives, felt that shortages were a greater risk to people with hemophilia.***

"Based upon current information, which do you think is a greater risk to people with hemophilia?"

All participants:	
vCJD	5%
Shortages of factor concentrates	95%
Patient groups only:	
vCJD	9%
Shortages of factor concentrates	91%

Minimizing Risk

Deferring blood donors who are at risk of being infected with vCJD has been the primary approach for minimizing the risk of vCJD in the blood supply. This was an issue that received much attention, given the U.S. Food and Drug Administration's recently revised guidance. However, speakers and participants addressed a variety of other issues, including steps in the manufacturing process of blood derivatives that remove TSE agents.

Dorothy Scott (U.S. Food and Drug Administration) discussed vCJD risks in donors, which were taken into account when the FDA developed new donor deferral guidelines. In predicting results of various deferral actions, different measures have different effects upon supply, but equivalent safety outcomes, she said. There was particular concern about the effect on plasma derivative supplies of a ban on donors who lived in Europe for five years or more. An exception to the pan-European donor deferral was made for donors of source plasma for plasma derivatives, she explained, because manufacturing of these products includes steps that have been shown experimentally to remove TSE agents.

In his presentation, Albert Farrugia (Australian Commonwealth Therapeutic Goods Administration and member of the WFH Task Force on TSEs) said that the FDA's policy has an enormous impact on regulators worldwide. He said it was reassuring that the FDA has made a distinction between fresh and fractionated products.

He also warned against limiting donor deferrals to Europe, pointing to the alarming arrival of BSE in Japan last year. Dr. Farrugia said it might be necessary to extend donor deferrals to people from other geographic regions. He suggested the most important question is not where there is BSE, but where it may be.

However, he highlighted the difficulty of limiting the unknown risk of vCJD through donor deferral, which leads to ever-increasing levels of product loss. He illustrated this point using the example of distribution of infected meat and bone meal (MBM) from the U.K. into Asia and other countries, which could introduce BSE in those countries.

During discussion, it was acknowledged that those countries that imported MBM from the U.K. are starting to see BSE in their own cattle. ***It was agreed that this is a risk and that entry of TSEs into the food chain needs to be studied more closely.***

Regulatory process

In reviewing the regulatory process, Dr. Farrugia noted that plasma products are very heavily regulated and dominated by the FDA in North America and the EMEA in Europe. He described the sector as "disproportionately regulated" given the actual risks involved, but conceded that this was a response to public pressure based on historical events.

In less-resourced countries, there is a tendency to accept the assessments and decisions of the FDA and EMEA; this is undesirable, Dr. Farrugia said, because it does not take into consideration important local issues and discourages the development of independent regulatory authorities. Regulation, however, plays only one part in issues around blood products; market forces are also very important.

There was a general call from participants for more harmonization.
However, during his presentation, Jan M. Bult (Plasma Protein Therapeutics Association) said harmonization of standards is a long way off, and called for debate in this area to be based more on science than politics. The introduction of new regulations has to be carefully balanced against the potential impact on supply, Mr. Bult concluded.

One of the recommendations from the first global forum was that the WFH prepare a regulatory guide to provide assistance to product prescribers, purchasers, and regulators. The guide is underway and will cover aspects of hemophilia treatment products, licensing arrangements, and guidance on good practices, and will include a glossary of terms. It is scheduled to be released in July 2002.

Communicating Risk

The issue of how to communicate risk was addressed from the point of view of patient organizations and treaters. The questions under discussion were how, what, and when to inform patients about risk. It was almost unanimously agreed that patients have a right to know if they have been exposed to contaminated blood products.

There continues to be wariness among patients about information coming from government and regulators, noted Gordon Clarke (European Haemophilia Consortium, a regional office of the World Federation of Hemophilia), who presented the results of a survey that he had conducted of national hemophilia organizations in Europe. He stressed that people with hemophilia want more direct information and more face-to-face opportunities to ask their own questions.

David Page (Canadian Hemophilia Society and WFH Vice-President NMOs and Youth) raised the question of what role a patient organization has in terms of policy decisions and assessing risk. He called on patient organizations to ensure consultation and to communicate with members about safety and supply issues. He called on blood authorities to open up to those who are most affected by policy decisions.

Paul Giangrande (Oxford Haemophilia Centre and WFH Vice-President Medical) and Simon Taylor (U.K. Haemophilia Society) gave two perspectives – the treaters' and the patient group's – on the issue of informing patients if they are exposed to vCJD-contaminated blood products. They recounted an incident last year involving hemophilia treatment products in the U.K. containing plasma from a donor who developed vCJD, and how the two groups dealt with informing and reassuring patients. Dr. Giangrande noted that future incidents such as these are inevitable, and the community must be prepared to deal with them.

At the end of the session, ***more than 90 percent of participants agreed that people with hemophilia who received contaminated clotting factor concentrate should be informed.***

"Given the current state of knowledge, do you think a person with hemophilia who has received a factor concentrate manufactured with plasma from a donor later diagnosed with vCJD should be informed of the fact?"

Yes	93%
No	7%

Supply Issues

The causes, effects, and long-term outcomes surrounding the recent product shortage were the main issues discussed. Participants also reported on the supply situation around the world and shared potential remedies for future supply crises.

By July 2001, Dr. Evatt reported, the shortages had grown so acute that many began to fear patients might die in emergency situations. However, inventories improved by November and Dr. Evatt projected that supplies would continue to rise through 2002. The situation, he concluded, underscored the need for open, frank discussions involving all concerned parties.

Mr. Bult addressed some of the difficulties of trying to predict shortages. The PPTA could only make predictions based on publicly available data, he said. Moreover, some things are just not possible to predict. Mr. Bult noted that manufacturing is only one stage in the process, and stressed the need to examine collection and product distribution issues as well.

Theo Evers (European Plasma Fractionators Association) contended that the limited number of recombinant product suppliers creates supply vulnerability, as does the dependency on the supply of starting material. Market mechanisms are not sufficient to ensure adequate product supply, and there is a real need for strategic provisions to reduce vulnerability and prevent shortages, he stressed.

H. Marijkeala van den Berg (Van Creveld Clinic-National Hemophilia Center) provided a treater's perspective on supply issues. Home treatment, prophylaxis, and longer life expectancies for people with hemophilia, coupled with safety concerns, have all contributed to increased demand for recombinant products, she said. She stressed the need to determine more exact information on dosage as well as to determine the cost-effectiveness and broader implications of specific therapeutic approaches.

The supply problems experienced in the developed world in the last year were put into perspective by Prof. Hu Ching-Li (Shanghai Second Medical University), who spoke on supply and treatment issues in China. Based on the estimated number of people with hemophilia requiring treatment, he said that China needs 2,775 million International Units (IU) of factor VIII concentrates annually. The number of units available is 15 million.

Providing a patient group perspective, Mark Skinner (National Hemophilia Foundation) said the situation caused by last year's shortages was a "sobering step backwards" for patients in the U.S. He cautioned against neglecting supply issues in future. Mr. Skinner recommended continuing to enhance the dialogue between regulators and manufacturers, and he warned that there is a real possibility of future shortages since the United States is still largely dependent on a single supplier for recombinants.

During the open forum session, facilitator Ashok Verma (Hemophilia Federation India) noted that worldwide

shortages caused by prophylaxis are created in the northern hemisphere, he said. Such shortages can be much more dangerous to the developing world although they originate from the developed world.

Participants discussed whether or not the recent supply crisis would lead to new thinking about modifying recommended dosages and the consensus seemed to be that it would not. Several participants said the shortage was an emergency situation that caused artificial reductions with potential detriment and little or no benefit.

Next steps

There was overwhelming agreement among participants that another global forum should be organized by the WFH to maintain dialogue on key issues for the global hemophilia community. The next forum is proposed for 2003.

**The WFH is grateful to its patron,
Jan Willem André de la Porte,
who provided funding for the
WFH Global Forum on the Safety and Supply
of Hemophilia Treatment Products.**

Session 1: Variant CJD – The State of Affairs

Opening Address

Dr. Peter Jones, WFH Executive Committee member and chair of the forum, welcomed participants and expressed his hope that this forum would be as productive and informative as the first WFH Global Forum on the Safety and Supply of Hemophilia Treatment Products.

Brian O'Mahony, President of the World Federation of Hemophilia, noted that the forum was a unique opportunity to look at sensitive and contentious issues, with open and constructive dialogue. He emphasized that the meeting's purpose was not to change views but to bring new perspectives and promote discussion.

Facilitator Simon Taylor of the U.K. Haemophilia Society outlined the procedure for group discussions. He explained that the WFH would publish proceedings of this forum, and noted that no comments other than the speakers' formal presentations would be attributed. He encouraged participants to be open and frank. Participants would have the opportunity to express opinions on a series of questions at various times throughout the forum using electronic voting system, he added.

To start off the forum, he asked the following questions:

With regard to the risk of transmission of vCJD via replacement therapy, are you:

Very concerned:	11%
Concerned:	62%
Not concerned:	28%

In the light of evidence currently available, do you believe that vCJD can be transmitted through the infusion of coagulation factor concentrates?

Non-patients only:	
Yes:	13%
No:	55%
Don't know:	33%
Patients only:	
Yes:	22%
No:	28%
Don't know:	50%

Experimental Transmission of vCJD Through Blood Components

Larisa Cervenakova,
The American Red Cross Holland Laboratory

Dr. Cervenakova presented the latest results of the Holland Laboratory experiments on transmission of vCJD. She began by stressing that there is no epidemiological or experimental evidence of vCJD transmission through blood transfusion or use of plasma-derived products. Moreover, Dr. Cervenakova said, the blood of animals with the natural transmissible spongiform encephalopathies (TSEs) – scrapie of sheep and bovine spongiform encephalopathy of cattle – has never been demonstrated to be infectious when inoculated into experimental animals, and the blood of experimentally infected laboratory animals contains significantly lower levels (105 times) of infectivity compared to the brain.

Previous studies of TSE infectivity in the blood of experimental mice were conducted using the Fukuoka-1 strain of human TSE, which originated from a patient affected with genetic form of TSE, called Gerstmann-Sträussler-Scheinker disease, Dr. Cervenakova explained, while her ongoing experiments used a strain of mouse-adapted vCJD. Evidence from the Fukuoka-1 strain experiments would be cited for comparison purposes, she said.

The experiment was designed by using brain of a mouse euthanized at the clinical stage of the disease (courtesy of Dr. Moira Bruce, Institute for Animal Health, Edinburgh, Scotland, United Kingdom) that had been previously inoculated intracerebrally and intraperitoneally with a 10% homogenate prepared from brain tissue of a deceased individual afflicted with vCJD. A new group of animals was inoculated intracerebrally with 1% brain homogenate from a vCJD-infected mouse. After 154 days the first animal from that group died from the disease and others showed signs of the disease. All mice were euthanized after 157 days following inoculation and their blood was collected and separated into components. Brain tissue was harvested and assayed for the presence of abnormal prion protein using immunoblotting assay.

It was interesting to note that the incubation period shortened upon secondary transmission of vCJD, said Dr. Cervenakova, just as it had in earlier experiments with other strains of TSEs, including BSE strain. Experimental data also indicates that the incubation period for Fukuoka-1 is much shorter than the incubation period for vCJD, regardless of whether Swiss or RIII mice are used.

Dr. Cervenakova further noted that the characteristic pattern of PrP^{27-30} (abnor-

mal, proteinase K-cleaved form of prion protein) from the brain of infected mice is specific for Fukuoka-1 and vCJD strain, and remains unchanged in Swiss and RIII mice.

Whole blood was divided into red blood cells, buffy coat, platelet-rich plasma, platelet concentrate, and platelet-poor plasma. All of these components were inoculated intracerebrally and intravenously, with the exception of platelet concentrate, which was only inoculated intracerebrally.

In mice inoculated with buffy coat from vCJD-infected mice at the clinical stage of the disease, Dr. Cervenakova observed, infection can occur at different times after inoculation. In animals inoculated intracerebrally, three of 17 mice developed the disease, while two of six animals inoculated intravenously developed the disease. Low levels of infectivity have been also detected in platelet-rich and platelet-poor plasma of clinically ill vCJD-infected mice using both intracerebral and intravenous route of inoculation.

Dr. Cervenakova compared data of this experiment with previous experiments, and found that the level of infectivity in buffy coat of vCJD mice is lower than in Fukuoka-1-infected mice.

Experimental TSE Transfusion Studies

Source of Inoculum	Recipient Species	Number of Transfused Animals	Number of Positive Animals	Study Conducted
spCJD	Chimpanzee	3	0	NIH
Fukuoka-1	Mouse	20	1	ARC & NIH
263K	Hamster	47HD 61LD	3 0	VAMC & ARC
BSE	Sheep	21	1	IAH, UK
vCJD	Mouse	62 HD[1] 32 LD[2]	ongoing	ARC

[1] - blood from animals inoculated with 1% brain homogenate
[2] - blood from animals inoculated with blood components

Analysis of combined data on blood transfusion studies from various laboratories was also presented by Dr. Cervenakova. In a historical study conducted at LCNSS, NIH (Bethesda, Maryland, U.S.A.) none of three chimpanzees transfused with units of blood from sporadic CJD patients developed the disease. Low efficiency transmission was achieved in experimental studies using rodents: one of 21 mice transfused with blood from Fukuoka-1-infected mice developed the disease; three of 47 hamsters transfused with blood from animals infected with high-dose 263K scrapie strain developed the disease, while there was no disease transmission by transfusion of blood collected from hamsters infected with low-dose of the agent. There was a report on transmission of the disease by transfusion of blood from a sheep experimentally (per orally) infected with bovine spongiform encephalopathy. Dr. Cervenakova reported that a number of mice were transfused with blood from vCJD-infected mice at the Holland Laboratory, but no data were available yet.

Data on Inoculation of Buffy Coat from vCJD-infected Mice

Blood Component/ Route of Inoculation	Dilution	# Infected / # Inoculated Animals	Post-inoculation Time (days)
Clinical Phase (23 weeks)			
Intracerebral	1:2	0/5	524
	1:6	3/17	560 term.
	1:40	0/15	496
Intravenous	1:4	2/6	524
	1:40	0/10	496
Preclinical Phase (17 weeks)			
Intracerebral	1:4	1/11	468
Intravenous	1:12	2/12	468

Dr. Cervenakova concluded that the data collected in the current study using vCJD agent are consistent with previously collected data using Fukuoka-1 and BSE agent. The infectivity levels in blood components of mice infected with vCJD do not appear to be different from that for the Fukuoka-1 strain. She also noted that the level of infectivity in buffy coat is higher than in plasma at the clinical stage of the disease.

Dr. Cervenakova looked forward to additional data, particularly from ongoing mice and primate studies, which she hoped would help answer the question of whether or not blood from patients with vCJD is infectious.

The Risk of vCJD in Blood Products – Global Regulatory Response

Albert Farrugia,
Australian Commonwealth Therapeutic Goods Administration and World Federation of Hemophilia

The main influence on the global regulatory response to vCJD, Dr. Farrugia contended, is the U.S. Food and Drug Administration's decisions and therefore it is necessary to examine the recently published Guidance for Industry.

According to the FDA Guidance: "…until suitable donor screening tests are available, the FDA is recommending interim preventive measures that we deem to be prudent based on the available scientific data and the evolving state of knowledge regarding these diseases." Dr. Farrugia described this as a "revolutionary" statement for a regulatory authority. He noted that the FDA appears to be saying that they may reintroduce the excluded donors once reliable screening testing is available. This, he maintained, is a modification of the standard approach of regulators, which is to have a tripod of measures composed of selection, screening, and inactivation of the relevant pathogen. This would result in a revision of current principles which may well be desirable.

The Guidance, he continued, also contends that the vCJD epidemic in the United Kingdom continues to increase. The most recent evidence, he noted, suggests that the vCJD epidemic is peaking and creates room for hopeful optimism that the worst of the crisis has passed.

Dr. Farrugia also presented evidence of the rates of BSE in Europe, contending that the BSE epidemic is not homogeneous, and varies from region to region. He noted that the rates of BSE in Switzerland had appeared to be falling in 1998, when the Swiss began to test apparently healthy cattle; that resulted in a large jump in the number of cases and created widespread public concern. However, he added, the rates appear to be falling again.

Dr. Farrugia presented a copy of an American Red Cross news release from January 18, 2001. He maintained that the American Red Cross's unilateral declaration of the need for further tightening of the ban on blood donors who had visited the U.K., France, and Western Europe forced the FDA to revise its position. That position was based on the prevalence of BSE in those particular areas. However, he insisted, the most salient question is not where there is BSE, but where it may be. Dr. Farrugia pointed out the alarming arrival of BSE in Japan last year.

It is inconsistent, he said, to exclude Japan from donor deferrals. He presented data on the level of exports of meat and bone meal from the European Union to other countries. There has been a high density of meat and bone meal penetration in Asia, Dr. Farrugia noted, which creates a potential for recycling of BSE-infected material. As a result, he reiterated, it may be necessary to extend donor deferrals to people from other geographic regions – a possibility that the FDA had already conceded, he added. This highlighted the difficulty of limiting the unknown risk of vCJD through donor deferral, which leads to ever increasing levels of product loss.

Dr. Farrugia also pointed out the lack of harmonization among regulatory authorities about what constitutes a "European" country. Political geography is having an effect on health policy, he said.

He said it is reassuring that the FDA has made a distinction between fresh and fractionated products. There is strong evidence that plasma fractionation eliminates high levels of TSE infectivity, he observed.

Dr. Farrugia presented a summary of the various measures for donor deferral, which are in place in various European countries. He noted that this information was available on the WFH web site.

vCJD in the UK

	Probable – still alive	Probable – awaiting PM	Confirmed	Total
2000 – Year to June	7	5	5	17
2001 – Year to June	10	2	5	17
2000 - whole year	5		28	28
2001 - whole year	9		20	29

BSE in Europe

	December 2000	May 2001	Dec 2001
Eire	561	638	811
Portugal	481	545	597
Switzerland	364	374	403
France	232	302	499
Germany	12	57	138
Spain	2	38	82
Belgium	19	27	65
Netherlands	6	14	25
Italy	0	14	50
Denmark	2	4	8
Luxembourg	1	1	1

Among the ongoing issues that regulatory authorities are still grappling with is the spread of universal leukocyte production of all collected blood, Dr. Farrugia said. This is driven by the idea that removing white blood cells will reduce the levels of infectivity, he explained. However, he contended that the evidence suggests that is not the case. Plasma processing creates cross-contamination issues because the blood product industry is global, he noted, which creates enormous implications for product supply.

Dr. Farrugia concluded by reminding participants that regulators react to events; they don't shape them. He also restated the enormous impact that FDA policy has on all regulators worldwide.

World Health Organization Activities on vCJD

Ana Padilla,
Health Technology and Pharmaceuticals Cluster, World Health Organization

Dr. Padilla described the World Health Organization (WHO) project for the development of international reference materials for the diagnosis and study of human TSEs (both spCJD and vCJD). It is a complex and difficult project, initiated in 1999 with the cooperation of various international partners and research institutes, she stated.

Dr. Padilla explained that she worked in a program dealing with quality assurance of biological products. The main interest was how to facilitate the development of detection tests for TSEs; this amplified the need for global harmonization in evaluating process validation data, and the specific need for reference reagents and reference panels. In recognition of those needs, the WHO formed a working group on international reference materials for the diagnosis and study of TSEs. The objective of that group is to prepare reference materials that will advance the development of diagnostic tests for TSEs.

Dr. Padilla outlined the specific terms of reference for the working group:

- the selection and characterization of candidate materials which could serve for the preparation of international reference materials;
- the development of protocols for calibration of those materials for WHO collaborative studies;
- the harmonization of procedures for the classification and nomenclature of PrP^{Sc} typing in human cases;
- and the examination of issues concerning the appropriate use of proposed reference materials.

Considerable progress has been made in the development of laboratory tests for the detection of the pathological PrP protein (PrP^{Sc}), Dr. Padilla said. However, she added that the predictive values of these assays in terms of TSE infectivity have not been independently confirmed. Therefore, a correlation with bioassays from animal models is still required. As a result of these factors, the group is currently considering several different types of reference materials. They include human TSE brain-derived materials (calibrated in a WHO collaborative study), rodent-adapted strains of TSE agents, human TSE blood-derived reference materials, and spleen-derived reference materials.

To date, the group has developed human brain homogenates that were prepared from samples taken from four brains supplied by the CJD surveillance unit in Edinburgh. One was from a neurologically normal subject, one from a vCJD patient and two from sporadic CJD patients. The homogenate has been divided into 2,000 vials and will be used in in vitro and in vivo assays, Dr. Padilla said.

Preliminary data indicate that the vCJD material is suitable for both in vivo and in vitro assays. However, both spCJD samples presented the unexpected coexistence of two different glycotypes (one Type 1, one Type 2).

Dr. Padilla explained that once the materials have been examined using a range of procedures, it will be possible to establish a correlation between in vitro and in vivo experiments (that is, the same reference material can be used). The material can also be used for calibration, by distributing the reference material to various laboratories conducting experiments.

A WHO collaborative study has also been undertaken to define a harmonized PrP^{Sc} detection protocol, Dr. Padilla stated.

The working group is also studying human TSE blood-derived materials, in order to facilitate the study of diagnostic methods and validation processes. Dr. Padilla observed that the development of blood reference material would be very difficult, because of the absence of the detection of infectivity of PrP^{Sc} in human blood. Rodent-adapted TSE strains provide another approach, but some difficulty remains as there is disagreement on the appropriate spike preparation used in various protocols.

The group has already initiated a harmonized protocol for the collection of blood from humans with CJD for use in the investigation of blood-based diagnostic tests, Dr. Padilla said. Consultations on the protocol are in progress.

Dr. Padilla summarized a number of other activities in which the WHO is currently involved, and invited participants to access more complete information at the WHO web site: http://www.who.int/biologicals.

Variant CJD – The State of Affairs from an Industry Perspective

Charles Waller,
Plasma Protein Therapeutics Association (Europe)

Mr. Waller began by stressing that industry takes all potential risk very seriously. Although the risk of vCJD is theoretical, it is being treated as a real threat and taken very seriously, he stated.

There is no evidence that people with pre-clinical or clinical CJD, including vCJD, carry infectious prions in their blood or have transmitted infectious prions through any blood products, Mr. Waller emphasized. There are numerous studies with classical CJD and various studies underway with vCJD, and none has indicated infectivity through blood products, he said. Mr. Waller cited two recent articles in the *Lancet*, reporting that researchers could not detect any infectivity in the blood of vCJD patients.[1,2] There is increasing circumstantial evidence that is encouraging, he added, while reiterating that industry continues to take all possible precautions.

The U.K. provides a microcosm of the overall issue, Mr. Waller said. Despite the use of U.K. plasma and many millions of transfusions, there is still no evidence of any vCJD transmission. He conceded that several patients who died of vCJD had received transfusions, but none of their infections was traced back to their donors. Moreover, there have been no cases of CJD or vCJD detected among recipients of blood or plasma from donors who were, subsequently, known to have vCJD. Mr. Waller stressed that to date, there has been no evidence in the U.K., where 99 percent of all cases of BSE and 96 percent of all vCJD have been reported, that vCJD has been transmitted through blood or blood products.

Mr. Waller noted that eight vCJD patients had received transfusions, but none had been traced back to a donor identified with CJD. Fourteen patients with vCJD donated blood and eight vCJD patients had their donations traced to 22 recipients, none of whom developed vCJD, he added. There have also been eight confirmed donations from vCJD patients that were pooled for fractionation; however, Mr. Waller noted that none of the thousands of product recipients has been identified with vCJD to date.

Despite the mounting evidence that vCJD is not transmissible through blood products, Mr. Waller reiterated, the industry continues to treat the theoretical risk as a real risk. The industry is taking numerous steps to ensure the safety and supply of blood products. These steps include the sponsorship of relevant research and the sharing of data, which Mr. Waller described as an important and positive development.

Beyond research, Mr. Waller said, the industry is attempting to communicate the most recent, accurate information as widely and comprehensively as possible, using workshops, direct mail, publications, and its multilingual web site (www.plasmatherapeutics.org). Industry's approach is to involve consumers and encourage the free flow of information to create a good understanding of the issues and challenges involved, he said. Various precautionary actions are being taken, but it is necessary to strike a balance between the competing demands of safety and supply, he concluded.

1, M.E. Bruce, I. McConnell, R.G. Will, J.W. Ironside (2001) Detection of variant Creutzfeldt-Jakob disease infectivity in extraneural tissues Lancet 358:208-209

2 J.D.F.Wadsworth, S. Joiner, A.F. Hill, T.A. Campbell, M. Desbruslais, P.J. Luthert, J. Collinge (2001) Tissue distribution of protease resistant prion protein in variant Creutzfeldt-Jakob disease using a highly sensitive immunoblotting assay Lancet 358: 171-80

The State of Affairs – Treater Perspective

Wolfgang Schramm,
Ludwig-Maximilian University Hemophilia Centre

Treaters want to help their patients while avoiding any potential problems for them, stated Prof. Schramm. He stressed the importance of taking responsibility for all hemophilia patients – not just the 20 percent who are well treated, but also the 80 percent throughout the world who receive poor treatment.

Prof. Schramm noted that there are currently more than 100 cases of vCJD in the U.K., three in France, and one in Ireland. Extrapolations using the current model, he contended, suggest that there could be hundreds of new cases in France and Germany in the near future through primary infection via the food chain. More alarmingly, it is still not known how and if secondary infections from human to human may occur, Prof. Schramm added. Data from the German Hemophilia Registry, which has been tracking patients since 1982, has still not seen any co-occurrence of hemophilia and vCJD, he reported.

Prof. Schramm described the strategy that has been adopted by the German authorities regarding vCJD. The transmission of vCJD via plasma seems unlikely, since the agent is almost completely eliminated during the production process. Even if the vCJD agent is transmissible via blood transfusion, the risk would be eliminated once a reliable screening test is developed, he said.

From a treater's perspective, it is critical to balance safety measures with supply concerns, Prof. Schramm said. There are various options to reduce the risk of vCJD transmission through transfusions. These include: the use of the safest pos-

sible blood products available (optimal use); the development of reliable diagnostic tests to screen blood donations for vCJD infection; the exclusions of some persons from the donor pool; and leukocyte depletion in the production processes of erythrocyte and thrombocyte products.

Concurrently, there are options that can ensure the provision of a sufficient long-term supply of blood and blood products, Prof. Schramm explained. These include: the critically indicated application of blood product (optimal use); promoting advertising for the recruitment of donors; motivation campaigns for donor recruitment; and the revision of exclusion criteria.

There is still no documented evidence of any person with hemophilia having classical or variant CJD, Prof. Schramm reiterated, despite many studies from the U.K., U.S., and other countries. Although it is never possible to create complete safety, Prof. Schramm contended that the blood supply is the safest it has ever been. Hemophilia is a life and limb-threatening disease which necessitates that real risks must be balanced, and that includes the risks attendant upon product shortages, he said.

Prof. Schramm urged participants to consider the degree of safety that is optimum, particularly in developing countries where supply is a serious issue and where it is often very difficult to collect sufficient donations to produce plasma-derived products.

Traditionally, he concluded, we measure cost-benefit and cost-utility in economic terms. It would be more meaningful if human issues such as quality of life became part of those equations, he said.

A Patient's Perspective of vCJD

Gordon Clarke,
European Haemophilia Consortium

Mr. Clarke presented the results of a survey that he had conducted of national hemophilia organizations. Although the survey was short and straightforward, only 12 member organizations responded, a response rate of only 29 percent, he commented.

There are several possible explanations for the low response rates, Mr. Clarke observed. A number of countries view the theoretical risk of vCJD as less important than how to access treatment "in real time." At the other extreme, there are a growing number of countries that have moved to a nearly 100 percent recombinant supply, so they're less concerned about blood-borne infections. Finally, many organizations just find themselves with too much to do and too few resources, he said.

Mr. Clarke presented a summary of the responses to his survey.

1. Do you consider your national member organization to be:

Very well informed?	2
Adequately informed?	9
Poorly informed?	1

2. From which sources have you received information?

Government	5
Hemophilia doctor	9
Other doctor	2
WFH/ EHC	12
Other (Internet, media, BPL)	5

3. Has the information been:

Timely?	8
Informative?	12
Comprehensive?	6
Understandable?	9

4. Are there other views you would like to hear?

WFH/ EHC	5
Scientists	7
Doctors	2
Regulatory bodies	7
Government	7
Other (pharmaceuticals, other countries)	2

5. What questions about vCJD are most frequently asked by your members?

- We get almost no reaction on this matter, probably due to almost 100 percent use of recombinant products.
- Are government, scientists, and doctors telling the truth?
- Why can't we all just have recombinant product?
- Is the product used in our country safe?
- Can we get certain assurance that product is safe to use?
- Is there any difference in safety between plasma and recombinant products?
- Are blood donors tested for vCJD?
- How dangerous is infection from blood products?
- Will vCJD be a problem like HIV in the future?
- Are there cases of vCJD in our country?
- What are the signs of vCJD?

6. What steps has your national hemophilia organization taken to distribute information to members:

Seminars/expert speakers	2
Newsletter articles	8
Explanatory letter	4
Agenda at members' meeting	6
Web site articles	7
Other (brochure, etc.)	1

Clearly, the message from patient organizations is to "keep the information flowing," Mr. Clarke said, and to improve the information exchange between countries. There continues to be wariness among patients about information coming from government and regulators, he noted. He stressed that patients want more direct information and more face-to-face opportunities to ask their own questions. Moreover, they want the information to be useful and understandable, and they want their national hemophilia organizations to do more to bring answers to their members, he stated.

Discussion

Simon Taylor summarized his impressions of the presentations. He objected to the use of the term "theoretical risk." To describe risks as theoretical, he contended, is to attempt to dodge the real issue. There is a risk – the matter for discussion is how big the risk is and what should be done about it, he said.

Mr. Taylor invited questions or comments from the floor.

One patient participant suggested that patients would feel more comfortable if each vial of treatment products or packaging listed the source of the plasma.

A regulator in the audience noted that plasma source is required information for every regulatory authority. However, others remarked that most patients have no access to regulatory data. Several participants expressed support for providing source information on every bottle.

A participant from a developing country said he was angry that U.K. meat and bone meal had been exported to so many countries, including Asia. He asked Dr. Farrugia if donor deferral policies should take into account people who have consumed these products. Dr. Farrugia replied that it should be a consideration. However, he noted that in all cases the exporters claim that the meat and bone meal was not used to feed cattle or livestock. He also noted that if the process were carried to its logical conclusion, all of those who may have consumed meat or bone meal at risk of BSE contamination would need to be excluded from donations, which means excluding nearly everyone.

Another participant expressed her surprise that people are so confident when they declare that there has been no evidence of vCJD transmission so far. She stressed that the time frame for research has been so short, that it is difficult to cite any reliable epidemiological evidence with confidence. She also questioned the efficacy of using spiking material for testing, suggesting that not enough is known about the actions of infective prions in the blood.

Other participants echoed her concerns. One noted that it is too soon to say, conclusively, that the results of real cases of vCJD patients are reassuring, while stressing that theoretical studies have been much less reassuring. Another audience member stressed that it is important not to become complacent. Remember the experience of hepatitis C, which remained dormant for years, he urged.

Mr. Taylor asked participants to reconsider the questions they answered at the beginning of the session, to see if the presentations had changed their perceptions in any way.

With regard to the risk of transmission of vCJD via replacement therapy, are you:

Very concerned?	13%
Concerned?	64%
Not concerned?	22%

In the light of evidence currently available, do you believe that vCJD can be transmitted through the infusion of coagulation factor concentrates?

Non-patients responded:

Yes:	12%
No:	53%
Don't know:	35%

Patients responded:

Yes:	43%
No:	29%
Don't know:	35%

Session 2: The Decision-making Process – A Question of Risk

Before introducing the speakers for the second session, Simon Taylor gave a breakdown of the participants at the forum: approximately 30 industry representatives, 20 medical practitioners, 20 patient groups, and 10 regulators.

Participants voted on the following questions.

Do you feel that CJD poses the same threat to the hemophilia community as HIV did in 1982?

Yes:	1%
No:	93%
Don't know:	3%

Do you feel that vCJD poses the same threat to the hemophilia community as HIV did in 1982?

Yes:	7%
No:	82%
Don't know:	10%

Is History Being Repeated? A Comparison of vCJD with HIV

Bruce Evatt,
Centers for Disease Control and Prevention and World Federation of Hemophilia

Dr. Evatt compared CJD and vCJD with HIV at similar points in their respective crisis timelines – HIV in 1982, CJD in 1998, and vCJD in 2001. He began by contrasting CJD with HIV. Dr. Evatt noted that HIV was a new disease in 1982, whereas CJD was an old one in 1998. At the time of each crisis, the disease was caused by an unknown agent; but the CJD numbers were stable, while the HIV numbers were increasing. HIV had an unknown incubation period, was present in people with hemophilia, and was known to be transmitted in blood. CJD had a known incubation period, it had not been detected in people with hemophilia, and there had been no known blood transmission. Knowing the incubation period is important to estimating the extent of the epidemic. Finally, HIV lacked animal models, while CJD does not. As more data accumulates, there is growing confidence that CJD is not being transmitted through the blood supply.

Dr. Evatt then compared vCJD with HIV, as well as with CJD, according to the same characteristics. During the crisis times, both vCJD and HIV were new diseases caused by an unknown agent, with increasing numbers of infected patients. Both diseases had unknown incubation periods. Despite the absence of human blood transfusion-transmission cases, vCJD – unlike CJD – appears to have a transfusion-transmission risk in animals. In addition, the vCJD agent is found in many more tissues of infected patients than is the CJD agent, including such tissues as lymphoid tissues, which contain blood cells. This presence of the vCJD agent is of particular concern in relation to the potential for blood infectivity, but further study is needed on prions in lymphoid tissue. Finally, the incubation period of vCJD is shorter in experimental animals than that of CJD, suggesting a more virulent organism than CJD.

The result of the comparison between vCJD and HIV is not as encouraging as that between CJD and HIV. Thus the estimation of the relative number of donors in the plasma pool, estimation of the titer of infectious agent in a donor, and potential for manufacturing processes to remove the agent are needed to further evaluate the risk of vCJD infection.

Dr. Evatt next discussed assumptions that scientists are following in their work with vCJD. It is predicted that the peak of BSE in Europe will occur between 2002 and 2005. The highest risk of plasma donor infectivity is in the U.K. and France, and possibly Japan. Current methods for producing factor VIII are expected to clear three to six logs of infectivity, and methods for manufacturing factor IX should clear seven logs, greatly increasing safety. To date in the U.K., eight donors with vCJD were traced to 22 recipients of blood products. None of the 22 has developed CJD.

In the developed world, concern is focused on product safety, while availability remains the number one issue in the developing world. "We are forced to live with the reality that we cannot make decisions on donor exclusions which eliminate all risk for all patients," Dr. Evatt concluded.

Assessing the Risk of vCJD: A Decision-making Model

Francine Décary,
Hema-Québec

Dr. Décary used the example of Québec, Canada, as a decision-making model for assessing the risk of vCJD. On October 15, 1998, a report from the Bayer Advisory Council on Bioethics on CJD was made public. Recommendation 20 stated, "That persons who at any time since 1980, have resided in a geographic area with a significant incidence of BSE or nvCJD not be permitted to contribute

blood or plasma until the hypothetical risk of accepting donations from such persons can be evaluated."

Canada's blood suppliers, Health Canada, and other stakeholders met to evaluate the situation. They made three observations: there was no current scientific evidence that vCJD could be transmitted by blood; deferring donors who had resided in the U.K. could create risk to Canada's blood supply; and the travel habits of Canadians were unknown. It was decided that a large deferral would be problematic, but a rapid loss of three to five percent of donations could be withstood. A survey of donors found that donors in Québec were less likely to have travelled to the U.K. than donors in the rest of Canada. Hema-Québec, the blood supplier for the province, felt comfortable that excluding these donors would not threaten the blood supply, Dr. Décary said.

In April 1999, it was decided to defer all donors who had spent a month or more in the U.K. since 1980. This would lead to a three percent loss in donations, which was judged an acceptable risk to the blood supply because it would bring a risk reduction of 70 to 85 percent. It was also decided to exclude from fractionation the plasma of any donor who had spent time in the U.K. since 1980. This would lead to a five percent reduction in plasma supply and a risk reduction of 100 percent for Hema-Québec plasma. In October 2000, the same approach was used for donors who had spent six months in France in the same period.

Dr. Décary described the governance framework for making such decisions, including risk management policy and decision-making policy implementation. The recommendation on the precautionary principle of the Commission of Inquiry on the Blood System in Canada, presided by Justice Krever, was the motor for decision-making. The recommendation calls for the principle of safety to transcend other principles and it also states, "The balancing of the risks and benefits of taking action should be dependent not only on the likelihood of the risk materializing but also on the severity of the effect if the risk does materialize, on the number of persons who could be affected, and on the ease of implementing protective or preventive measures. The more severe the potential effect, the lower the threshold should be for taking action."

She concluded: "Taking into account that the vCJD challenge was presented to the new operators of the blood supply in Canada just two weeks after their startup, it is important to recognize the contribution of Justice Krever's recommendation 2(e), which has served as a template to make decisions in the context of uncertainty."

Risk Assessment from a Hemophilia Organization's Perspective

David Page,
Canadian Hemophilia Society, and
World Federation of Hemophilia

Mr. Page asserted that hemophilia organizations have a unique role to play at all stages of the risk assessment process by:

- identifying issues that are important to users of blood and blood products;
- consulting with those who have the most to gain or to lose as a result any eventual decision;
- contributing to the analysis and adoption of policies that are consistent with the priorities of the population; and
- communicating with patients and the public in ways that they can understand.

Who does a hemophilia organization represent? The first constituency is its members, but Mr. Page also questioned the organization's responsibility to other disease groups and the public in general. "Can a hemophilia organization demand action to minimize risk to its own members, knowing that this could increase risk to others?" He concluded that a hemophilia organization must consider the effects of its actions on broader policy issues while not losing sight of its primary responsibilities. It is worthwhile to build coalitions with other blood-user groups to share knowledge and skills.

He highlighted the importance of building up its expertise and credibility in the blood system. Hemophilia organizations

What are the risk assessment issues a hemophilia organization is concerned with?

- The relative safety and efficacy of factor products, both plasma derived and recombinant
- Ongoing surveillance of current products, for example, with regards to CJD
- Emerging pathogens such as vCJD, hepatitis G, TTV, SEN-V
- Notification procedures (or the lack of them) in the event of a recall or withdrawal of blood products
- Donor screening procedures
- New tests for blood donations, such as NAT, and the high costs attached to them
- Availability of plasma and how this is affected by various policy decisions
- Availability of factor products and how this can be affected by regulatory actions

must make blood safety and supply issues a top priority internally, Mr. Page said. He recommended cultivating a core group trained and informed on the issue, and ready to work with other stakeholders.

Maintaining credibility is difficult, especially with one's own members, he noted. Because of HIV and hepatitis C, many people with hemophilia now believe that no matter how remote the threat, it will become a reality. Mr. Page discussed the case of a Utah donor diagnosed with CJD in 1998. Some products using his plasma were sent to Canada. Health Canada originally quarantined all implicated blood products, then released the products on Christmas Eve, with the support of the Canadian Hemophilia Society (CHS), based on its assessment that the risk of classical CJD was minimal. However, medical and scientific opinions on the actual level of risk were split and many patients reacted in panic. The CHS was accused of caving in to the pharmaceutical industry. The CHS spent six months trying to put the risk into perspective, Mr. Page said.

The CHS actions were based on scientific risk analysis as well as a set of values: transparency, autonomy of the person, and greatest benefit, least risk. "The challenge is to focus on the real risk. Hepatitis B led us to underestimate HIV. HIV blinded us to hepatitis C. Now vCJD is absorbing us, while 75 percent of people with hemophilia in the world go without treatment," he said. Moreover, "many of those that do receive care are treated with cryoprecipitate that is not even virally inactivated." Mr. Page concluded by calling on the blood authorities around the world to open up to those who have the most to lose from any policy decision.

A Regulator's View of Risk and Risk Assessment (EMEA)

Manfred Haase,
Paul Ehrlich Institut and the European Agency for the Evaluation of Medicinal Products (EMEA)

The principal purpose in the regulation of medicinal products is to make available safe and effective products, of good quality, which provide benefits that outweigh their risks, stated Dr. Haase. This is easier said than done, because it is difficult for licensing authorities to make such a judgement.

Dr. Haase discussed risk analysis as it applies to determining the level of acceptable viral risk. Risk analysis is a scientific evaluation of the probability of occurrence and the magnitude and severity of the effect. In areas of uncertainty, such as emerging threats, risk analysis is a difficult but necessary exercise. Where uncertainty exists, a precautionary approach should be taken. Precautions must be proportional to the degree of uncertainty and take into account the expected benefits of the product. This is complicated, and a science-based approach is warranted, said Dr. Haase.

Benefit-risk assessment for individual medicinal products takes into account general public health issues and individual patients. Immunocompromised individuals and children should get particular attention. In the evaluation of products, the objective of the quality data is to demonstrate that a product of good and consistent quality is produced, and that potential safety issues arising from manufacture are avoided or minimized.

Safety information will be derived by extrapolation from non-clinical data and from the overall experience with the use of a new medicine. Evidence of efficacy is provided by clinical studies. Ensuring safety in special populations means investigating risk for different patient groups, he stated.

In Europe, sites where products are manufactured have to hold a marketing authorization and have a satisfactory recent inspection showing compliance with good manufacturing practice (GMP). The Committee for Proprietary Medicinal Products (CPMP) may request good clinical practice (GCP), good laboratory practice (GLP), and pharmacovigilance inspections. At the time of granting a marketing authorization, there is a substantial body of data on the product's quality, safety, and efficacy. The size and validity of the database is crucial, said Dr. Haase, while noting that the quality of inspections in Europe is improving.

There should be a balance between the need for clinical data to evaluate risks prior to marketing authorization and the avoidance of delays in making available efficacious medicinal products to patients in medical need. Clinical trials give more substantial assurance on efficacy compared to safety, as a very large number of subjects are required to rule out rare adverse reactions.

During clinical trials, populations are defined by strict inclusion and exclusion criteria. Larger and less-well-defined populations are likely to be exposed to products with time. The larger exposure will lead to adverse reactions and interactions.

Risk Assessment from a Regulator's Perspective (FDA)

Dorothy Scott,
FDA Center for Biologics Evaluation and Research

A major challenge of risk assessment is weighing the risk of disease transmission by products versus the risk of limited supply, especially in a worldwide context, stated Dr. Scott. Another pitfall is

the tendency to interpret results of risk assessments as facts. Risk assessments should estimate the worst case, but should also provide outcomes for a range of assumptions. Assessing the cost of taking precautions to reduce risk, e.g. "collateral damage," is also a challenge.

Dr. Scott discussed vCJD risks in donors. It is entirely unknown whether human blood is capable of vCJD transmission at a low frequency. Estimates of how many people may be at risk of having vCJD may not be precise, due to lack of information about the vCJD epidemic. Some unknowns include incubation time, and distribution of vCJD in the population. The highest numbers of cases are in the U.K. and France, and are related to beef consumption. Food chain controls are important in preventing humans from contracting vCJD, she stated. The role of secondary exposure through the blood supply is unknown at this time.

She then reviewed the FDA's risk assessment process leading up to the new donor deferral guidelines. The precautionary principle has no status in U.S. law, Dr. Scott said, but it is especially applicable where adverse effects may emerge long after exposure, and when risks that are carried forward into the future cannot be eliminated or reduced except at the time of exposure.

In predicting results of various deferral actions, it was found that different measures had different effects upon supply, but equivalent safety outcomes. The evaluation of donor deferral scenarios helps regulators to optimize safety measures, while minimizing the chance that dangerously low supplies will occur. In addition to new donor deferral guidelines, the U.S. encouraged a national donor recruitment campaign and instituted a system to monitor adequacy of the blood supply.

There was particular concern about the effect on plasma derivative supplies of a ban on donors who lived in Europe for

Donor Deferrals: Phase I (British beef exposures) Anticipated Implementation May 31, 2002

- ≥ 3 months residence in U.K. 1980 - 1996
- ≥ 5 years France 1980 - present (vCJD cases; 5-10% British beef consumption)
- ≥ 6 months on certain military bases (up to 35% British beef consumption)

Donor Deferrals: Phase I Anticipated Implementation May 31, 2002

- Transfusion of blood, platelets, or plasma in the U.K. 1980 - present
- Transfusion-transmission: small, still short-term lookback studies negative now; single BSE/sheep experiment positive; prevalence vCJD in U.K. unknown but could be high

Donor Deferrals: Phase II Anticipated Implementation October, 2002

- ≥ 5 years residence/travel Europe, 1980 – present
- European countries: USDA 21 CFR xxx (Oman not included; Gibraltar added)
- New additions to list by guidance
- ** Source plasma donors not deferred **

five years or more. Furthermore, plasma derivative manufacturing includes steps that have been shown experimentally to remove TSE agents. Based upon these factors, an exception was made to the pan-European donor deferral for donors of source plasma for plasma derivatives.

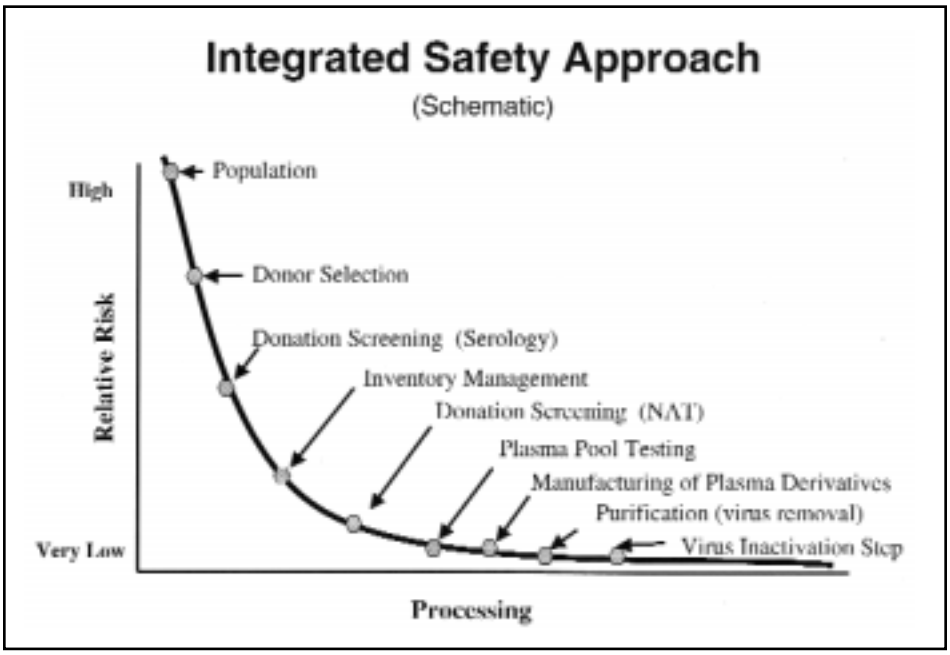
Risk Assessment – Industry Perspective (PPTA)

Jan M. Bult,
Plasma Protein Therapeutics Association

For industry, dedicated donors are central to risk assessment and the decision-making process, Mr. Bult said. Initiatives by the Plasma Protein Therapeutics Association (PPTA) and industry to include appropriate donor groups have included public education, working in a robust regulatory environment, good centre location, the use of well-crafted questionnaires, employment of experienced professionals, state-of-the-art testing technology and deferral of donors who spent time in certain geographic locations.

Mr. Bult questioned practices that he has seen with mobile public sector collection units operating at campsites in France where donors had to wait in the heat for a long time. PPTA initiatives include a donor motivation campaign, and using plasma from North America and Europe for fractionation. The use of an "inventory hold period" means that donations can be traced and rejected up to 60 days after collection as the result of post-donation information.

Mr. Bult then discussed nucleic amplification technology (NAT). The advantages of NAT are reduction of the virus-related window by early detection of highly viremic donations. Methods for the inactivation and removal of pathogens have to be effective, validated, and robust, Mr. Bult stated. PPTA has collaborated with others in the scientific and regulatory communities to support improved validation. In the years to come, new standards for NAT will come, providing standardized technology and language.



Quality control and quality assurance are extremely important. PPTA members have used a third-party review to ensure that the correct systems are in place, and this adds another layer of protection. Manufacturers are responsible for active pharmacovigilance, traceability of products, batch recall standards operating procedures, and patient notification. An example is the Patient Notification System as it currently exists in the U.S.

International harmonization of regulatory requirements is a long way off, Mr. Bult said. He called for the debates in this area to be more on science than politics. He cited the decision in Japan to defer any donor who had lived in a country with significant BSE, or one case of vCJD, or an increase in TSE. This decision was made before BSE was found in Japan. He wondered whether the implemented policy will impact the collection practices in Japan. Other countries potentially face a similar conundrum, as the extent of the spread of BSE becomes clear.

Regulatory requirements and voluntary industry initiatives together ensure that today's plasma protein therapies have achieved the highest margin of safety ever. Risk of transmission is negligible for enveloped and non-enveloped viruses, and remains theoretical for vCJD. The introduction of new regulations has to be carefully balanced against the potential impact on supply, Mr. Bult concluded.

Discussion

Simon Taylor initiated the discussion, which focused on the trade-off between measures that are intended to increase safety, and their impact on supply.

A clarification was requested on the case of the Utah donor. David Page said albumin from the donor was used in the preparation of recombinant factor VIII. There was also clarification on the concept of holding donations before using them.

It was noted that the donation rate in Canada and Quebec is not high in comparison to other countries. The blood suppliers in Canada are looking at how to do a better job of recruiting. Recruitment of donors is a "soft science"

but an essential part of the industry.

The concept of a plasma master file has not yet been accepted worldwide. On the issue of whether there is disharmony between deferral criteria, it was suggested that there is no disharmony on minimum standards, although some nations make a choice to exceed those standards. There was more discussion on balancing risk and the different views of scientists and patients.

Participants cast opinions on several questions.

Do you feel that vCJD poses the same threat to the hemophilia community as HIV did in 1982?

Yes	5%
No	88%
Don't know	7%

Are current risk assessment models used in making decisions on vCJD more scientific, more political, or balanced?

All forum participants:

More scientific?	17%
More political?	33%
Balanced?	50%

Are current risk assessment models used in making decisions on vCJD more scientific, more political, or balanced?

Producers only:

More scientific?	13%
More political?	31%
Balanced?	56%

Are current risk assessment models used in making decisions on vCJD more scientific, more political, or balanced?

Regulators only:

More scientific?	20%
More political?	40%
Balanced?	40%

Should current restrictions on donors for vCJD be:

Strengthened?	14%
Reduced?	27%
Remain the same?	59%

Session 3: Current Supply Issues – Recombinant and Plasma Product Shortages

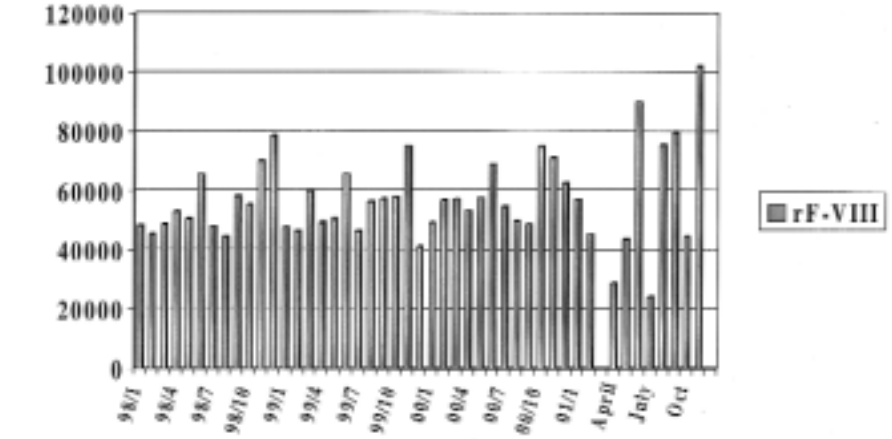
Industry Perspectives (PPTA)

Jan M. Bult,
Plasma Protein Therapeutics Association

Mr. Bult began by revisiting a number of industry responses to global product shortages that he had raised at the last WFH Global Forum, in April 2000. At that time, he suggested the possibility of harmonization, the continued use of "plasmatics," improved margins of safety, increased use of recombinant products, more continuity in supply, and increased use of prophylaxis. While some of those predictions came true, he noted, some of them were incorrect – particularly the predicted supply continuity and increased use of recombinant products.

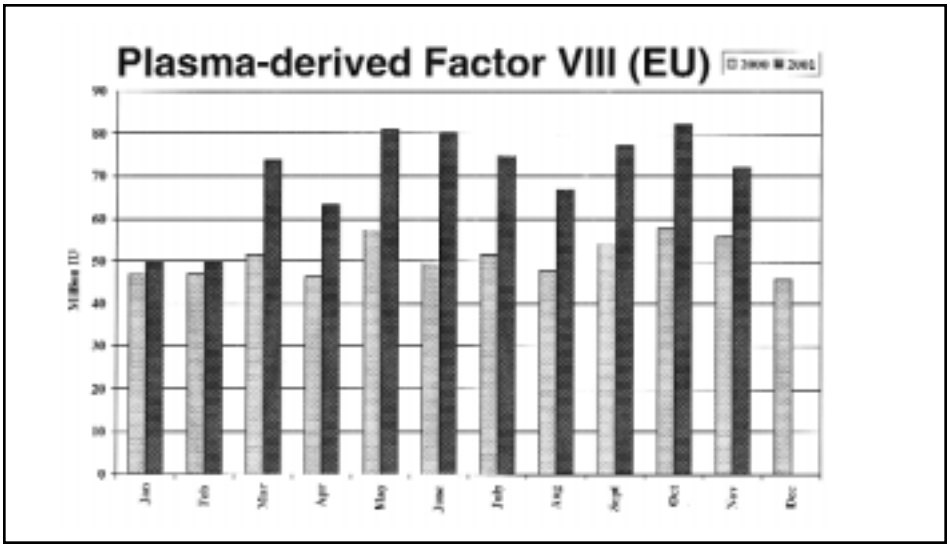
No one is happy about the shortages of the last year, Mr. Bult stated. One of the industry's first responses was to ensure that the products that were available were delivered as quickly as possible to consumers. In addition, the industry increased production capacity, increased fractionation of plasma-derived products, and held multiple meetings with consumers and government agencies. The rate of data collection was increased to twice per month, and as much information as possible was shared publicly through various publications and the Plasma Protein Therapeutics Association (PPTA) web site.

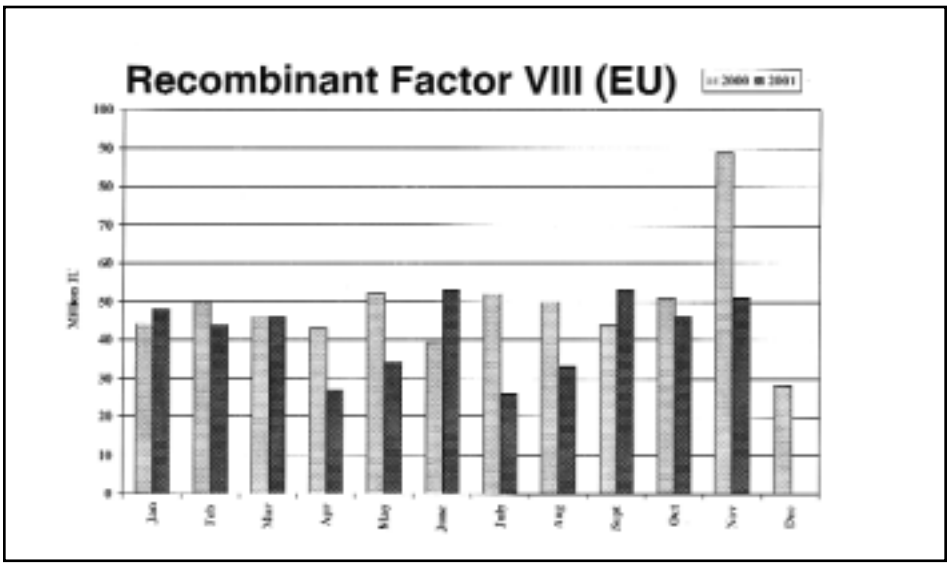
Mr. Bult provided detailed information on the evolution of the supply fluctuation in 2001. The shortages became evident in North America in April 2001; the

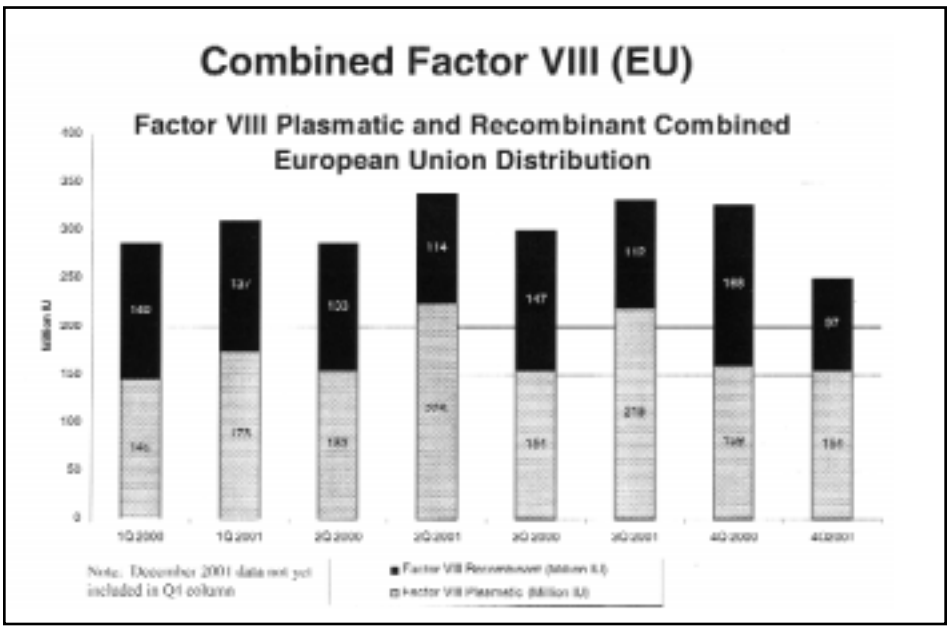


Mid-month Collection

	High Purity 1 – 15	High Purity Month	Recombinant 1 – 15	Recombinant Month
January		23,576		57,275
February		22,365		45,139
March	11,884	39,527	suppressed	suppressed
April	16,349	37,177	suppressed	28,585
May	20,557	58,983	23,683	43,724
June	27,382	54,577	39,660	90,022
July	10,382	34,664	10,459	24,164
August	16,109	33,799	34,368	75,416
September	10,806	42,867	20,865	79,751
October	9,853	40,170	7,698	44,305
November	15,382	25,634	41,708	102,486
December	24,960		43,376	







production of plasma-derived factor VIII was increased to address it. Throughout the period, consumers were provided with information as quickly as possible. The situation in Europe mirrored that in North America, with distribution of plasma-derived factor VIII increasing, while recombinant product decreased. In fact, the overall consumption of recombinant products was higher than plasma-derived products in Europe during 2001.

The supply shortages did lead to some consumer benefits, particularly more timely information that contained more accurate real numbers, Mr. Bult said.

He addressed some of the difficulties of trying to predict shortages. The PPTA could only make predictions based on publicly available data. Moreover, he admitted, some things are just not possible to predict. He also noted that manufacturing is only one stage in the process, and stressed the need to examine collection and product distribution issues as well.

Patient groups and government organizations want the industry to take certain measures to guarantee supply, said Mr. Bult. However, he maintained, anti-trust laws make it illegal to facilitate information exchange because U.S. law doesn't allow manipulation of the market, price-fixing, or production and output agreements.

On behalf of the industry, Mr. Bult pledged to continue to provide as much information as possible and to keep improving product quality. He concluded by stressing that industry had come to realize that, for patients and treaters, it is more helpful to provide bad news than no news at all.

Industry Perspectives (EPFA)

Theo Evers,
European Plasma Fractionation Association

The European Plasma Fractionation Association (EPFA) is the international association of not-for-profit manufacturers of plasma products. Its aim is to ensure continuity of supply of safe and high-quality products, and promote voluntary non-remunerated donations and community self-sufficiency. It is committed to the sharing of information and transparency, Mr. Evers said.

The EPFA works in collaboration with the European Blood Alliance, and its membership comes primarily from the public health sector. The primary goal of the EPFA members continues to be providing products in EPFA member countries, using starting material collected regionally or nationally from voluntary non-remunerated donors, he said. In addition, many members are currently exporting surplus products.

During the current supply crisis, EPFA members managed to provide a continuous supply of plasma-based products. There are currently major concerns about supply of plasma and plasma products in Europe, as there are in most parts of the world. Despite European Directive 89/381 in which regulators encouraged self-sufficiency, few initiatives have been taken to increase the supply of blood and plasma from voluntary unpaid donors.

The European Union Blood Directive is legislation regarding the quality and safety of blood and blood product collection, testing, processing, and distribution. As a result of recent shortages, supply issues have become part of the debate around the directive, Mr. Evers explained.

At the beginning of the recombinant supply shortage, there was uncertainty about the probable duration of the shortage. The initial responses focused on modifying treatment regimes. Although there was early reluctance to switch to plasma-based treatments, the length and severity of the shortage led to broad consultations with patients, treaters, government, and industry, and subsequently led to increased demand for plasma products.

In response, there was an increase in output by EPFA members of as much as 15 percent, although the ability to increase production varied depending on the country or member organization. EPFA members succeeded in providing sufficient product to meet immediate demands, Mr. Evers noted.

The different measures taken in different markets to overcome the shortages had consequences in other markets. Mr. Evers contended that the limited number of recombinant product suppliers creates supply vulnerability, as does the dependency on the supply of starting material. Market mechanisms are not sufficient to ensure adequate product supply, and there is a real need for strategic provisions to reduce vulnerability and prevent shortages, he stressed.

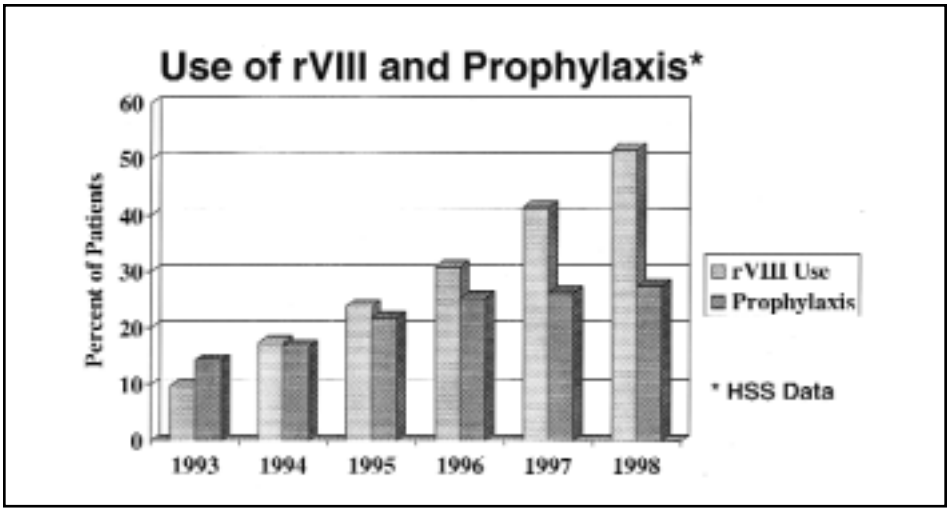
Some countries have succeeded in increasing or achieving self-sufficiency in product and plasma supply. It is possible and advisable, Mr. Evers concluded, for regional authorities like the European Union to recognize the need for strategic provision of products, and to provide appropriate frameworks within which all parties can collaborate to accomplish that goal.

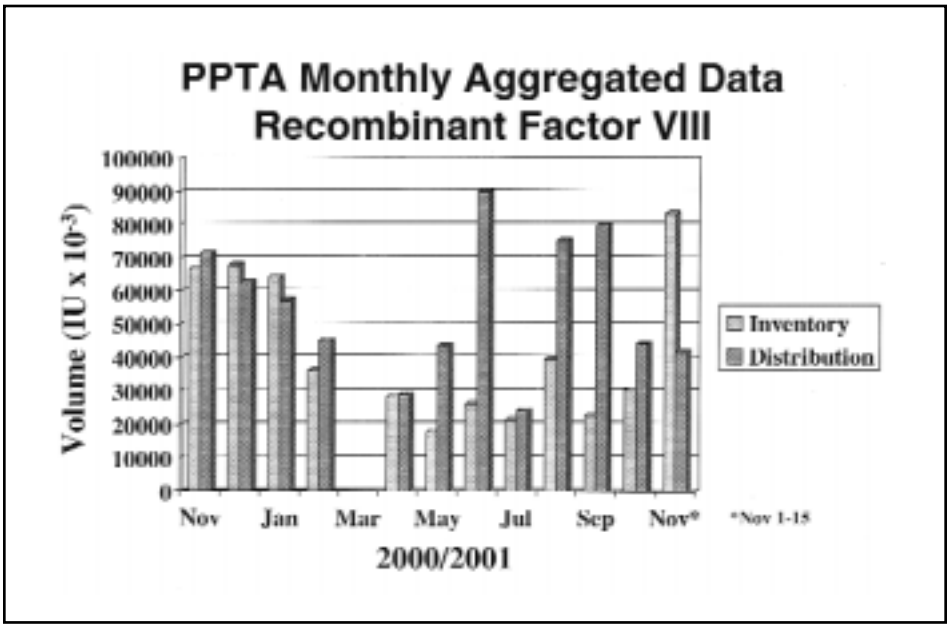
The Influence of the Shortage of Recombinant Products on Treatment

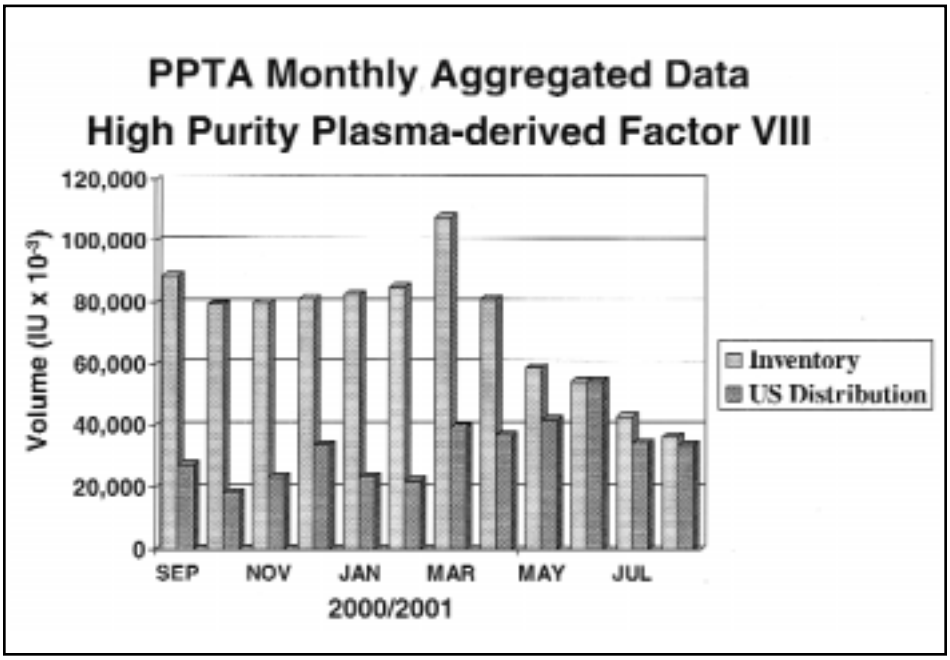
Bruce Evatt,
Centers for Disease Control and Prevention and World Federation of Hemophilia

Dr. Evatt outlined some of the causes of blood product shortages in the United States in 2001. One cause was the increased use of primary prophylaxis. Other causes included temporarily reduced global access to recombinant (resulting in increased use of plasma-derived factor VIII), the increased use of secondary prophylaxis in older children, and more elective surgeries.

One reason for the increased use of primary prophylaxis was a greater number of patients on long-term prophylaxis. The impact of this greater number has been startling. More than three-quarters of people with hemophilia use blood products; half of these patients use on-demand therapy and account for one-third of the use of factor VIII in the United States.







The other reason for the increased use of clotting factors involves high doses. A small number of patients (fewer than three percent) are on extremely high doses of immune-tolerance therapy.

Also during 2001, a number of manufacturing and production problems made it difficult to obtain certain types of clotting factors in the United States. The effects were felt worldwide, with countries that depend entirely on external supplies experiencing shortages of up to 30 percent. Countries with internal supplies also saw shortages, from 10 to 20 percent.

In discussing the shortages, Dr. Evatt presented the findings of a survey conducted among hemophilia treatment centres (HTCs) in the United States. The number reporting difficulty in obtaining recombinant factor VIII peaked in mid-2001. Between 60 and 80 percent of HTCs responded to the shortage by switching patients to plasma-derived factor VIII, while half delayed or reduced prophylaxis. Guidelines issued by the National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC), which outlined recommended conservation strategies, assisted in reducing patient demand for clotting factor by 20 to 40 percent.

By July 2001, the shortages had grown so acute that many began to fear patients might die in emergency situations. To contend with this possibility, a workshop was held by the Centers for Disease Control and Prevention to try to organize an emergency system for delivering clotting factor to deal with life-threatening emergencies.

Dr. Evatt commended the industry for its diligent work in overcoming difficulties in manufacture and distribution. Inventories had improved by November, although plasma-derived factor VIII remains in short supply. Dr. Evatt projected that supplies would continue to rise through 2002 and noted that even during the extreme shortages, there were no reports of any patients remaining completely untreated. The situation was multifaceted, he concluded, and underscored the need for open, frank discussions involving all concerned parties.

The Perspective of the Hemophilia Treater

H. Marijkeala van den Berg,
Van Creveld Clinic-National Hemophilia Center

Dr. van den Berg began by noting that clotting factor concentrates have changed the lives of people with hemophilia dramatically and that with a sufficient supply of therapeutic products, their life expectancy has become normal. Near the beginning of the development of cryoprecipitate, there was a close relationship between patient, doctors, donors, and the local blood bank. This relationship, however, disappeared with the development of concentrates and the

situation further changed in the 1980s when regulators like the FDA and EMEA came into place and developed safety guidelines.

The patient used to be at the centre of the process and all the people and institutions involved in her/his care were located nearby. The current scenario places industry at one end of the process with donors in the middle and patients, doctors, caregivers, and the WFH at the other extreme. Safety was the main factor in increasing the distance between patients and producers, she said.

The rapid development of safer, ultrapure recombinant products and the stricter regulation of blood products have been major factors in increasing cost, Dr. van den Berg explained. Home treatment, prophylaxis and longer life expectancies for people with hemophilia, coupled with safety concerns, have all contributed to increased demand for recombinant products, she said. This is particularly true in the developed world.

At the same time, increased distances between supply and patient made national overview more difficult. Given that 55 percent of the European patient community is on recombinant product therapy, the shortages were a big issue, especially in countries where there was a lack of plasma-derived clotting factors. Choices made in Europe depended on local situations, she stated.

Since recombinant product is the treatment of choice, it is traditionally used to treat children whenever possible. Consequently, children were the first to be affected by the shortages. The problem was compounded because small vials were often unavailable, resulting in waste.

The shortages led to the suspension of immune tolerance treatment and the cancellation of orthopedic surgeries. Furthermore, the shift in demand for plasma-derived products created severe shortages in the developing world. Dr. van den Berg warned that the rescheduling of cancelled orthopedic and elective surgeries could create new shortages in the future.

She concluded by asking participants to carefully consider the implications of an industry-driven environment and the correlation between extremely high safety standards, high price, and lower availability. She stressed the need to determine more exact information on dosage as well as to determine the cost-effectiveness and broader implications of specific therapeutic approaches.

Patient Organization Perspective (U.S.)

Mark Skinner,
National Hemophilia Foundation

Last year's shortages caused a total shift in the treatment "mantra" in the United States, said Mr. Skinner. The principles of treat when in doubt, be independent of our treaters, and treat early, were thrown out the window, he said. Patients found themselves tethered to their physicians for the day-to-day management of their conditions, he said. The situation, normal for patients in much of the rest of the world, was a "sobering step backwards" for patients in the U.S.

There has been such a focus on ensuring the safety of products for so long, that supply monitoring issues were neglected, Mr. Skinner said. Patients want to understand what happened, how, and why. While there is no benefit in apportioning blame, it is necessary to understand the situation to prevent it from recurring.

Information sharing is still very limited and tends to be retrospective. A valuable lesson could be learned by analysing what happened at Berkeley with Bayer. There is no doubt that Bayer's problems were the largest precipitating cause of the crisis. Many opportunities to address the shortages were lost because people did not have the necessary information in time.

Mr. Skinner recommended continuing to enhance the dialogue between regulators and manufacturers. He warned that there is a real possibility of future shortages since the United States is still largely dependent on a single supplier for recombinants.

He recommended an increased commitment to accelerated licensing of new fractionation plants in times of crisis, and a variety of data collection devices at all levels (including the consumer). An emergency distribution system needs to be put in place, which will guarantee prompt access to clotting factors in critical situations.

He concluded by expressing his concern that payers might respond to this period of "sub-optimal" care by refusing to insure the previous levels of therapy.

Patient Organization Perspective (Malaysia)

Norhanim Asidin,
Hemophilia Society of Malaysia

Malaysia did not experience the same product shortages described in other countries, said Dr. Asidin. Since 1975, there has been a centralized National Service Centre in Kuala Lumpur, which houses the central registry for hemophilia and congenital bleeding disorders. The centre is also a WFH-accredited International Hemophilia Training Centre.

Malaysia's goal is to establish a pool of non-remunerated voluntary donors, safe from transfusion-transmitted diseases, and to ensure the highest quality and safety in screening and testing procedures. The plasma collected from these donors is made into contract-fractionated products, mainly factor IX, in which Malaysia is self-sufficient. Production of factor VIII, albumin, and immunoglobulin still only meets about 20 percent of demand, requiring importation of products to make up the difference.

Most cases are treated on demand. There is very little prophylaxis. Factor VII is only used to treat certain cases with inhibitors. All treatment at the National Service Centre is free, supported by the government.

Since 1985, there has been a shift from using cryoprecipitate and plasma to a total dependence on factor concentrates. That shift has raised real concerns when there is a world shortage of clotting factors. The country has experienced shortages of two products, generally imported from the U.S. To counter this, Malaysia has increased production of factor concentrates, which are manufactured through a contract fractionation program, and is attempting to increase the collection of blood and plasma in provinces outside of Kuala Lumpur. All collection is administered by a central authority.

Although no shortages have been experienced to this point, there continues to be great fear about the security of future supply, she concluded.

Patient Organization Perspective (Brazil)

Maria Foshi Nivia,
Unidade de Hemofilia-Hospital Brigadeiro

Dr. Nivia explained that she was making the presentation on behalf of Brazilian Federation of Hemophilia President Maria Cecilia Magalhaes Pinto, who was unable to attend. Hemophilia is a difficult disease to manage, compounded by the need to deal with complications from treatment as well as the disease. Safety and supply of treatment products are universal issues.

In developing countries, the challenges of securing adequate supplies are more important than guaranteeing "absolute" safety. It is important not to forget past experiences with contamination, Dr. Nivia said, but "real safety is the guarantee of supply with no further threats."

When recombinant products were developed, the expectation was that they would be free of contamination and the risk of inhibitors with unlimited production capacity. In reality, the supply can affect safety and there are limitations to production capacity.

Three-quarters of people with hemophilia worldwide suffer from inadequate treatment, suffering pain, isolation, and premature death. Most of those patients are in the developing world.

During the recent supply crisis, the shortage of recombinant products in developed countries led to increased use of plasma-derived products and resulted in dire consequences in developing countries. Acute as shortages were in places like the U.S. and Europe, they paled in comparison to those felt in much of the rest of the world, she stressed.

Brazil's geography and demographics create particular challenges; 75 percent of the population live in rural areas and there is very low population density in northern areas. The Brazilian Ministry of Health has created a hemophilia subcommittee to oversee the treatment of over 7,000 registered patients in 27 states. The government's priorities are normalization, product purchase, distribution, and consumption administration. The regional hemocentres are a "blood network" that covers the entire country; however, some regions (such as the Amazon) are still poorly serviced.

The objectives of the Brazilian Federation of Hemophilia are to ensure patient safety and adequate supply. The organization provides an interface between patients, physicians, government, and industry. The critical goal for Brazil and the rest of the developing world is to provide quality products in sufficient quantity, she concluded.

Needs Assessment of Factor VIII Usage in China

Hu Ching-Li,
Shanghai Second Medical University

Dr. Hu stated that he sees the issue of shortages from a different perspective than the other presenters. China has a huge territory (9.6 million square kilometres) with nearly a quarter of the world's population. He contrasted the population of the city of Shanghai (13 million) to Switzerland (6 million) in an effort to illustrate the challenge that "sheer magnitude" creates.

The population and territory of China are so large that it has not been possible to carry out an accurate survey of people with hemophilia. There are no official data related to the number of hemophilia cases in China. A survey in Anhui province estimated that the prevalence of hemophilia A was five per 100,000 population. However, Dr. Hu cautioned that this figure could be inaccurate. If the WHO-estimated world incidence of one case per 10,000 population applies, the expected number of hemophilia patients should be 127,000, and the number of severe and moderate cases should be 79,300. Yet, there are only 5,000 registered cases. This indicates the extent to which hemophilia is undiagnosed and untreated in China, he said. The large gap also points to China's critical need for help from international organizations like the WFH.

If the need for factor VIII is estimated according to the WHO recommendation for dosage levels and the estimated number of people with moderate and severe hemophilia A, 2,775 million units of factor VIII would be needed annually. However, there is no way that China could afford that level of treatment, so practitioners make do with lower dosages. In fact, the whole country consumes only 15 million units per year.

There is no prophylaxis in China, he said. The price of factor VIII treatment is only US$0.15 per unit, but it is still beyond the reach of most patients. The facility in Shanghai has the capacity to triple its production, but hasn't bothered because so few can afford treatment. Similarly, the recommended frequency of prophylaxis treatment in China is only once per week (the WHO recommends three treatments per week), but it is still too expensive for most.

Recently, there has been alarming news about HIV in China, with 28,000 reported cases and estimates of as high as 600,000 cases. This is creating concerns about the safety of transfusions, he reported. It is reassuring that there have been only 10 known cases of CJD and none of vCJD in China. However, the presence of BSE in Japan is disturbing since it is so close to China, and is giving rise to new concerns about vCJD and other communicable diseases. The lack of a good regulatory body combines with these other issues to create a completely different perspective in China, which Dr. Hu urged participants to consider.

Session 4: Open Forum Discussion

The purpose of the open forum discussion period was to provide participants with the opportunity to discuss anything related to the safety and supply of hemophilia treatment products, said Simon Taylor. Glenn Pierce, of the National Hemophilia Foundation in the U.S.A., and Ashok Verma, of Hemophilia Federation (India) and WFH Executive Committee member, facilitated the session.

Dr. Pierce asked the forum to vote on the following question:

Do prions cause vCJD?

Yes	87%
No	13%

The results were interesting, Dr. Pierce said, adding that we only think we understand vCJD. If vCJD is not a concern, he said, what will come next and how will it behave? We don't know where the next CJD-like agent will come from, he concluded.

In response, a participant suggested that there is excellent evidence linking prions to infectivity. There is as yet, no method sensitive enough to test for prions in blood or plasma. Perhaps in the future, a threshold will be determined, and unsafe products will be identified with more certainty.

Dr. Pierce asked if the solution is to be found in having stricter deferrals, or finding new ways to inactivate and eliminate the virus. A participant suggested that even if measures could be used to allow lifting of deferrals, this might not happen. For example, the screening for hepatitis C is quite good but intravenous drug users are still deferred.

Another participant likened doubting the link between prions and vCJD to governments claiming that they don't know what causes AIDS. There may not be proof but there is enough evidence to make responsible decisions possible, the participant said.

It was noted that prions can be cleared by partitioning. Another participant suggested that although prions are the likely culprit, there is still a possibility that vCJD may be a virus.

Another audience member argued that it is a mistake to trust any one mechanism for ensuring blood safety. Removing any components of the process could open the back door for agents to adapt and come back, he warned.

A scientist suggested it is important to correlate removal of prion proteins (PrPs) with bioassays. This will provide reassurance of the efficacy of processes to remove infectious agents, and will necessitate the use of surrogate or actual viral agents.

Brian O'Mahony noted the extremely varied list of donor deferral systems. He said the FDA and EMEA are world leaders in developing deferral guidelines balancing safety and supply. He urged that harmonized minimum standards be developed. He also said that local decisions have to be made on how many donors would be lost to each deferral. For example, Ireland can safely defer Japanese donors but the deferral of anyone who had lived in the U.K. would be disastrous because of the loss of donors.

Many participants agreed with a call for regulators and stakeholders to come up with some harmonized standards. It was noted that the WHO is looking at convening a consultation to look at harmonization sometime later this year.

There was some discussion of the political and social issues connected to donor deferrals and beef in Europe. It was noted that decisions on safety of blood and meat supplies are intimately linked with political gamesmanship. There are also emotional factors associated with both blood and food that make these issues complex.

Given the tons of meat and bone meal (MBM) shipped from the U.K. throughout the world, a participant asked, does vCJD now exist in countries which have yet to report it? It was acknowledged that those countries that imported MBM from the U.K. are starting to see BSE in their own cattle. Other factors play a role, such as how meat is processed, and the genetic makeup of the population. It was agreed that this is a risk and that entry of TSEs into the food chain needs to be studied more closely. To date, clinical vCJD has only been detected in the U.K. and France. It seems that vCJD is a disease of consumption of British beef products.

Noting the appearance of BSE in other countries, a participant asked why the FDA does not defer donors who spent time in those countries. The FDA is looking at the possibility of deferrals for Japan and other countries, replied another participant. This issue is made more complex because there is poor data on how contaminated MBM was used; for example, which countries were merely transit points, and which nations were end-users. Food chain control is obviously essential. Recycling of the epidemic can be prevented by not using MBM to feed cattle.

There was discussion on whether countries like the U.S., which are thus far free of BSE, should adopt the highest standards to protect themselves. Such a decision could involve a costly trade-off

in terms of supply for safety. In reality, a participant suggested, the U.S. has a more conservative approach than Europe.

Participants discussed how the U.S. might respond when the first BSE-infected cow appears. It is not inevitable that one cow would lead to deferral of 250 million donors, a participant asserted. There are other issues that would need to be looked at.

A participant asked which held the greater risk – a vial of factor VIII made from pooled plasma in Europe, purified and viral inactivated, or eating fried sausages from pooled European meat products three times a week.

One response to this question was that people are known to have contracted the disease from eating meat, while there is no known case of transmission through blood products. In the U.K., hemophilia patients have taken products known to be contaminated with vCJD without developing the disease. Therefore, eating the meat has a higher risk associated. Most scientists seemed to agree that taking the concentrate would be less of a risk than eating the sausages.

A participant asked about the theoretical risk of contracting CJD through blood products, and the possible risks of recombinant products. It was noted that there has been a drive to eliminate albumin from recombinants but questions of stability have now arisen. Recombinants and other alternatives are not risk-free. There is a lack of clinical experience in this emerging area.

Another participant observed that medications are approved even when death is a rare side effect. Attempts to have zero-risk in blood products are based on a double standard, she said.

Mr. Verma shifted the discussion from safety to supply and gave a developing world viewpoint. Actions in the developed world are not always rational from a global perspective, he stated.

Worldwide shortages caused by prophylaxis are created in the northern hemisphere, he said. Such shortages can be much more dangerous to the developing world although they originate from the developed world.

Simon Taylor said the statistics the forum had heard on the problem in China were humbling.

A participant asked if the recent supply crisis had led to new thinking about modifying recommended dosages for less wasteful use of products. Several participants said the shortage was an emergency situation that caused artificial reductions with potential detriment and little or no benefit. Concern was also expressed about a secondary shortage occurring when supplies are back up and procedures that have been postponed are rescheduled. The challenge is phasing back into normal practice without creating a second crisis, a participant said.

It was suggested that some patient groups in the developed world misuse factors VIII and IX. Little is known about adequate dosages. The issue of vial size still needs to be studied. The developed world has work to do on rationalizing the use of concentrates, one participant stressed.

A participant cautioned that any move to reduce dosage could have a negative effect in developing countries. Another audience member noted that usage in Europe varies from 1.5 units per capita in Greece to 7.6 units in Sweden. No developing country even comes close; many are between 0.01 and 0.4 units per capita.

There was a suggestion that the WFH develop a database reflecting prices worldwide. It was suggested that this would pressure producers to harmonize their prices. It was noted that the shift to the euro has meant greater price transparency in Europe. WFH Executive Director Line Robillard said that the WFH has started collecting global pricing data. Efforts to gather and disseminate this information will continue.

It was noted that the price charged by the manufacturer is different from the price paid by or for the patient. While having this data is helpful, it does not tell the whole story.

A participant pointed out that blood products are regulated differently from other pharmaceutical products. It was suggested that any increase in standards requires higher investment by manufacturers. There are also practical issues associated with risk assessment. It was possible to ban fractionation of U.K. plasma but not possible to ban the use of cellular blood components. Another participant disagreed with claims that more testing would require higher investment, pointing out that hemophilia products are profitable; they drive growth for companies and have high margins.

Cutting out the middlemen was proposed as one way to control prices. However, even reducing prices will not make a difference for most people with hemophilia since they rely on their governments to pay for treatment. No matter how low-priced products become, they will still be unaffordable to a large proportion of people with hemophilia.

It was suggested that the crisis in North America last year was caused by regulatory policy being driven by politicians who demanded certain restrictions, not the FDA. It was also noted that industry, in seeking a competitive edge, may make unfounded claims about the relative safety of a product. This was seen in 1996 with the introduction of NAT.

A participant called for transparency in the development of guidelines.

Participants voted on the following questions:

Based upon current information, which do you think is a greater risk to people with hemophilia?

vCJD	5%
Shortages of factor concentrates	95%

Based upon current information, which do you think is a greater risk to people with hemophilia?

Patient groups only:	
vCJD	9%
Shortages of factor concentrates	91%

Session 5: Communicating Risk - The Example of vCJD

The U.K. Experience – Treater Perspective

Paul Giangrande,
Oxford Haemophilia Centre and World Federation of Hemophilia

Dr. Giangrande spoke about the treaters' experience of communicating risk, illustrated by a U.K. incident last year involving hemophilia treatment products containing plasma from a donor who developed vCJD. He explained that he and Simon Taylor would discuss two different perspectives on the incident: that of treaters and that of the patient group.

On December 14, 2000, notification was received that plasma from a donor diagnosed with vCJD had been supplied to Bio Products Laboratory (BPL) in 1996 and 1997. The plasma had been fractionated into several batches of different products including albumin, immunoglobulin, and factor VIII and IX concentrates. By the time the notification was received, all products were past their expiry date and presumed to have been used in clinical practice.

Dr. Giangrande noted that a similar problem had occurred with factor VIII in 1997. At that time, the advice from the National Blood Authority to doctors was not to inform patients. The NBA stated, "the general view is that patients will not benefit from this knowledge." This position was reached because there is no evidence that blood products transmit vCJD, and no diagnostic test or preventative treatment. Also, it was felt that the news would cause "unjustified worry" and "create permanent blight on their lives, e.g. life or health insurance." At most, about 300 people in the hemophilia community were directly affected, he said. None of the factor concentrate was used abroad, but the immunoglobulin and albumin were.

In general, directives from the Department of Health are managerial and should be followed, Dr. Giangrande stated. The British hemophilia care community decided to force the issue. They knew that it was not an option not to inform. The cat was out of the bag and the only questions remaining were how, when, and what patients should be told. Treaters anticipated a wave of pressure when the story broke in the media. Dr. Giangrande said he would have preferred to inform patients in person at their six-month review, but since waiting meant risking that patients would find out from headlines in the media, this was not possible. The two options considered were a full and frank disclosure up front, or an offer to inform.

After some debate over informing all patients and asking them if they wanted confirmation, it was decided to inform only those patients who had received the batches. In the end, each hemophilia treatment centre (HTC) made its own decision on how exactly to inform. Letters were prepared which emphasized the lack of evidence of transmission of vCJD and the fact that BPL plasma-derived concentrates are now made from imported plasma. An effort was made to ensure that letters did not arrive on Friday so people would not be calling their HTCs over the weekend when no one would be there.

Dr. Giangrande highlighted what he felt was positive about the response to the incident, including rapid dissemination of news to the hemophilia treaters by BPL and the National Blood Authority. Specific information about implicated batch numbers was quickly tracked down and made available. Doctors in the U.K. responded quickly to try to provide a coordinated response and engaged in positive dialogue with the U.K. Haemophilia Society.

On the negative side was media attention, which was generally unhelpful and unwelcome. It was not possible to achieve unanimous agreement on a response amongst physicians. News was imparted to patients in an impersonal fashion: typically, by letter. Unaffected patients were only reassured after some time, causing unnecessary worry. It was virtually impossible to trace recipients of other products such as albumin and immunoglobulin.

Dr. Giangrande said that most patients handled the crisis well but he is aware of two patients who have had lasting psychological problems because of the incident. There has been increased pressure to switch to recombinant products. Some scheduled surgical procedures were cancelled because, despite the lack of evidence, recipients of the batches were rather arbitrarily viewed as being high risk.

Dr. Giangrande concluded with the warning that it is not a question of what if this sort of incident will happen again, but when.

The U.K. Experience – Patient Association Perspective

Simon Taylor,
U.K. Haemophilia Society

Mr. Taylor then discussed the same case from the point of view of the patient organization. Hemophilia treaters gener-

ally responded well, he said. He paid tribute to BPL for its ethical decision to inform the hemophilia community quickly.

Patient groups were concerned about the U.K. Department of Health policy of non-disclosure. Emotions were high because of the sensationalist media interest in BSE and vCJD on the heels of a four-year public inquiry. There was a high probability of a leak to the media.

Patient groups were interested in maintaining the trust of the hemophilia community. Complicity in a cover-up was not an option. They also wanted to counter the inevitable alarm that would be generated by the media. Patient groups supported hemophilia centres as the primary source of advice to people with hemophilia but wanted to provide an additional trusted source.

The U.K. Haemophilia Society (UKHS) sent a letter to all members timed to coincide with the treatment centres' letters. There were problems because some letters did arrive late in the week, and the help-line is not staffed on weekends. The UKHS felt that they had a duty to inform all people with hemophilia of the incident. They were concerned that there was no uniform or standard communication by the hemophilia centres. Not all hemophilia centres could be trusted to communicate the message to patients. Anecdotally, Mr. Taylor said that the smaller centres, which tend to lack long-term corporate memory regarding HIV and hepatitis C, were less communicative than the larger centres.

The UKHS database needed some work to make sure that letters weren't sent out to children. This should have been a "fail-safe" backup to communication from the hemophilia centres, but in many cases it was not.

Regarding the responses of people with hemophilia to the incident, Mr. Taylor said that older people were more philosophic. Those who were already angry about blood safety crises just got angrier.

Mr. Taylor said the greatest distress was among parents, particularly those who had recently switched their children to recombinant products. There was also the fear of discrimination and actual incidents of discrimination. One child was called "mad cow" in school.

Mr. Taylor said that future incidents such as this case are inevitable. Speaking as a public relations consultant who specializes in crisis communication, he said, it is important to remember, "You will be asked what did you know, when did you know it, and what did you do? So tell the truth, tell as much as you can, and tell it as quickly as you can."

Discussion

Participants then asked for elaboration from Dr. Giangrande and Mr. Taylor on details about the incident. Most centres communicated with all their clients but some offered the choice to not know if someone had received a bad batch. Mr. Taylor said that patients would be asked at their six-month review if they want to be informed in the future.

The news did not leak to the media until the end of January, after the letters went out. There was an effort to coordinate the letter from the UKHS with letters from treatment centres. This was not always successful. It took time to track down the information about who to contact, and it was a race to do a responsible job before the media got wind of the story.

A participant asked why people with hemophilia were denied surgery noting that eating meat is a quantifiable risk while evidence of a CJD risk from blood products is still unclear. "Are those who eat meat exonerated? Why are people with hemophilia singled out?" Another participant agreed but noted that people with hemophilia are generally not denied surgery. It was noted that even with the use of disposable equipment surgical procedures are not without risk.

There are other users of blood products who were not informed of their exposure to risk, a participant said. Some people outside the hemophilia community were informed but thousands were not. Patients who have a national society are easier to contact.

A participant told of a patient notification system instituted in his country four years ago, which allows people to register to be notified. It is voluntary and is intended to protect privacy. It was noted that databases for such purposes need constant refinement so that they are always ready for use.

It was noted that in quality control questionnaires, patients are asked what they know about their own status. Denial is a common part of the human condition. Full disclosure and reiteration are necessary. Patients have a right to direct knowledge in real time, but patients also have a right to choose not to be informed.

One member of the audience asserted that a voluntary system works but it is not the full solution in and of itself.

A participant from Canada praised the response of British treaters and patient groups to the crisis. He said he hoped Canadians would respond in the same way in a similar situation. A standardized bar-coding system would help in tracking recipients of bad batches, he suggested.

Nurses are a vital link in the communication chain, another participant asserted. The nurse must have the information before the patient. Nurses with training as counsellors are on staff at British comprehensive care centres.

An audience member said the decision to inform is quite easy if one were to put oneself in the patient's position. It is important that the patient and family understand the risk. Clearly, it would also be right for all recipients of suspect blood products to be informed.

One participant said spreading information on vCJD, as the WFH TSE Task Force does, is seen by some as spreading panic, however, he does not accept the argument that ignorance is bliss. Another agreed, noting that the Department of Health philosophy is insulting paternalism.

One participant said the entire BPL incident could have been avoided. Before the products in question were used, there was a campaign for all patients to be on recombinant products. The government denied funding for recombinant factor VIII and so patients were exposed to these products.

Mr. Taylor and Dr. Giangrande said they would be happy to share more about their experience as well as the text of the letters that were used.

Participants voted on the following question:

Given the current state of knowledge, do you think a person with hemophilia who has received a factor concentrate manufactured with plasma from a donor later diagnosed with vCJD should be informed of the fact?

Yes	93%
No	7%

Session 6: Global Regulatory Assessment of Products

Review of Assessment Processes Worldwide

Albert Farrugia,
Australian Commonwealth Therapeutic Goods Administration and World Federation of Hemophilia

Dr. Farrugia noted that plasma products are very heavily regulated and dominated by the FDA in North America and the EMEA in Europe. He described the sector as "disproportionately regulated," given the actual risks involved, but conceded that it was a response to public pressure based on historical events.

In less-resourced countries, there is a tendency to accept the assessments and decisions of the FDA and EMEA; this is undesirable because it does not take into consideration important local issues and discourages the development of independent regulatory authorities, Dr. Farrugia said.

Regulation, however, plays only one part in issues around blood products; market forces are also very important.

Every regulatory agency has essentially the same primary goals: safety, quality, and efficacy of products. With plasma derivatives, these concerns are addressed through facility licensing, the promotion of good manufacturing processes through pre-market product assessment, and surveillance of the product's performance after it is marketed.

There are various agencies involved in regulation and the evolution of regulation in Europe. They include the European Union through the common market, its general legislative structure, and the promotion and use of the new currency. The Council of Europe, which is distinct from and much broader than the EU, also plays a role, as do governments and agencies in the individual nations.

Dr. Farrugia reviewed the applicable legislation and its evolution within the framework of the oversight of medical products:

- 1965: The EEC instituted the regulation of proprietary medicinal products. (Directive 65/65/EEC)
- 1975: This regulation was amplified with standards and protocols for proprietary medicinal products. (Directive 75/318/EEC)
- 1975: Set up the CPMP and administrative measures for 65/65/EEC and 75/318/EEC products (however, all three of these measures excluded medicinal products derived from human blood). (Directive 75/319/EEC)
- 1989: Extended earlier regulations to blood products (Directive 89/381/EEC)

Actual formal oversight of blood and plasma products in the EU came relatively late in the day, Dr. Farrugia said. In 1975, the principles set out in the directives of 1965 and 1975 were acknowledged as being applicable, but not entirely adequate, for medicinal products derived from human blood or plasma. A subsequent directive in 1989 incorporated new details for oversight across Europe. However, Dr. Farrugia noted that regulatory oversight of transfusion has not been centrally administered in Europe – it has been limited to large-scale production of fractionates, and not donors or other issues.

Near the end of 2000, a new draft directive set standards for quality, safety, processing, and distribution of products, which would effectively create authority over the whole process. Dr. Farrugia noted that while there were national requirements in place before 2000, they were not nearly as comprehensive as the draft directive.

Some serious issues have arisen over the 2000 draft directive. One surrounds the requirement that blood and plasma products be from voluntary and non-remunerated donors, even if the product has been imported. Dr. Farrugia said although he personally endorses voluntary, non-remunerated source product, this requirement could have a serious impact on therapeutic access and would restrict products significantly. The world supply is so dependent on the U.S. plasmapheresis sector – which is not voluntary and non-remunerated – that this regulation could create a snowball effect culminating in worldwide shortages, he said.

In response to those concerns, the draft was amended and now stresses the need for testing, quality management, and a Europe-wide surveillance system, while supporting the ethical position that voluntary, non-remunerated donations are preferable.

Europe also uses a plasma master file concept. This is a system that documents the epidemiology of donors, sources, and testing procedures. The EMEA uses centralized procedures for products that involve high technology or high risk, Dr. Farrugia explained. Other products go through a mutual recognition standard whereby they are accepted after the assessment of other regulated European nations.

An important element of the European regulatory structure is an exemption in cases of "exceptional circumstances." That flexibility is especially important

for hemophilic products which require flexibility to ensure life-saving supply continuity.

By contrast, in the U.S., blood products have always been regulated under the Virus, Serum and Antitoxin Act of 1902. In the 1970s, control of biologics switched from the National Institutes of Health to the U.S. Food and Drug Administration.

Generally, the FDA's responsibilities are similar to those of the EMEA. It provides basic regulatory oversight, product evaluation and research, and houses massive resources for oversight. The FDA Center for Biologics Evaluation and Research (CBER) oversees a wide range of products, primarily through Title 21 of the Code of Federal Regulations (CFR) and a series of guidance documents. These guidance documents are developed with input from academia, government, and industry, and through public consultation.

Dr. Farrugia conceded that there has been criticism levelled against the use of voluntary guidance documents, rather than legally binding legislation. However, in practice, he maintained, the FDA is so powerful and legal liability so substantial, that it is rather difficult for industry to ignore them. Moreover, the use of guidances allows the FDA to move more quickly than following a legislative route in many cases.

The CFR specifically applies to human albumin, plasma protein fraction, and immunoglobulin. Special procedures apply for certain advanced technological products, including recombinant and synthetic therapeutic products. However, licensing of all therapeutic products is still required.

Assessment of Products Not Licensed by the FDA and the EMEA

Terry Snape,
Pharmaceutical Consultant

Dr. Snape spoke of how procedures and regulations impact on products, and what has to be done outside of Europe and the U.S. to gain some of the benefits of regulation.

He agreed with Dr. Farrugia that the basic goal of regulation is to ensure the safety, quality, and efficacy of plasma products. Regulators are necessary, he contended, because "over the years many people have made mistakes that have harmed the people they were trying to help."

Dr. Snape outlined several examples:

- In 1937, in the United States, a contaminated cough syrup killed over 100 people.
- In 1959, in Europe, the "thalidomide tragedy" resulted in thousands of fetal abnormalities.
- In 1966, in Europe, thyroid tablets containing salmonella were released.
- In 1972, in the United Kingdom, contaminated intravenous fluids caused six deaths.

In terms of blood products, there have been too many examples of incidents involving plasma products. There is a real need to look at the root causes of those incidents to learn the lessons necessary to make the supply of blood products safe, Dr. Snape said. The root causes varied. Some incidents were caused by products that did not undergo viral elimination or viral inactivation. Some were caused by the failure to use good manufacturing practices, and some involved poorly designed products. In addition, there is always the possibility of new infectious agents.

Dr. Snape asked participants to consider whether the focus on viral safety was appropriate or "obsessive." He compared recent data on fatalities from transfusion-transmitted infections (TTIs) to fatalities from medically incorrect blood transfusion. It revealed that only three percent of fatalities in 1998/99 were from TTIs. While we know that transfusion-transmitted infection is a serious issue, it needs to be put in perspective, he said.

There is a danger that stakeholders in this process will treat TTI as the only issue to be considered, he warned. Plasma products, without exception, are sterile products manufactured aseptically, he observed. There is no terminal sterilization process; consequently safety is totally dependent on the quality of the manufacturing process to deliver a product that will not transmit bacterial infection, or cause endotoxic effects or other problems. Assurance of the quality and safety of plasma products involves the assurance of plasma quality, through a validated process that incorporates viral elimination or viral inactivation. Therefore, there needs to be monitoring, oversight, and testing at all stages in the process.

Dr. Snape emphasized that good manufacturing practice must be ensured at the plasma centre and in the fractionation facility. Various factors can help minimize risks, including the exclusion of donors, mandatory serology testing on all plasma, exclusions based on post-donation information, and nucleic acid amplification testing (NAT). The process of safety assurance continues at the fractionation lab, with pool testing using viral marker tests and NAT. Samples are sent to national regulatory authorities for testing, and traceability back to the donor is maintained.

The process must be robust. Good manufacturing practices are developed to ensure that poor practice does not lead to the release of bad products, he said.

Dr. Snape questioned the value of finished product testing by third-party laboratories. He acknowledged that people have concerns that something might be missed or that a product could become re-infected after manufacture. However, he contended that post-production testing is essentially a marketing tool to allay public fears and has little real value. It is "a knee-jerk reaction without practical value," he said. The tests were not developed for use on finished products and typically produce inconclusive results, he asserted.

National regulatory authorities are attempting to establish and maintain systems of licensing and control. The licence is essentially a contract between the manufacturer and governments. Inspection and enforcement ensure that the contract is respected, and require appropriate quality systems.

Some common features of established regulatory provisions include:

- the review of data in the marketing application, especially plasma quality commitment through plasma master files, process and batch testing, and the review of safety, efficacy, and pharmacokinetic data;
- the inspection and enforcement of the plasma donor base, the manufacturing process and facility, and the storage and distribution network;
- control batch review and release;
- post-marketing surveillance and follow-up.

In regions where there is no formalized regulatory system, agencies responsible for blood products must act and be seen to act, Dr. Snape said. Individuals in those scenarios will lack experience and resources, he conceded. The playing field is not level and agencies, particularly in developing countries, have difficulty paying for expensive monitoring and testing processes. In those countries, there are often several generations of product concurrently available and the benefits of choosing one over another are not always very clear. Guidance is essential, he said.

Variability in quality of plasma used for products is inevitable. How can the regulator make judgements in the absence of information? The regulators in these cases cannot know if the collection and manufacturing process has been safe and if the product is high quality. Moreover, they need to respond to changing circumstances that are entirely beyond their control since product price and availability are driven by events in the U.S. and Europe, Dr. Snape noted. He added that there is a perception that the most recent product is probably the best one, but that is not necessarily the case.

In many countries, there is great pressure to choose products on the basis of price alone. However, Dr. Snape stressed that political expediency does nothing to ensure safety, quality, or efficacy. In some cases, it might be easier to work through a broker, but he noted that transparency is lost. Many of the laboratories involved are not properly qualified to conduct the tests; samples are often too small for reliability and the tests have not been designed for finished products.

Although the challenges facing non-FDA and non-EMEA regulators are substantial, Dr. Snape maintained there are some measures that can be taken. He recommended developing direct, managed relationships with suppliers; selecting products that have been licensed by established regulatory authorities; using pre-contract questionnaires; and auditing suppliers. He cautioned against using pre-shipment data as the primary source of information and reiterated the importance of auditing batch expiration information. Finally, he encouraged people in these situations to ask for help when they lack the resources to do things themselves.

The WFH Regulatory Guide

Terry Snape,
Pharmaceutical Consultant

Dr. Snape explained that he had been asked to assist in the development of the "regulatory cookbook," recommended by participants at the last WFH Global Forum. The guide is intended to provide assistance to product prescribers, purchasers, and regulators by providing information that is current, definitive, and helpful.

While attentive to FDA and EU process, the guide is targeted to less-regulated environments. It will cover factors contributing to the quality, safety, and efficacy of hemophilia treatment products, and guidance on good practices in inviting tenders and evaluating products. The guide will provide an overview of established regulatory systems and include a glossary of terms. The guide stresses the importance of considering plasma source and processes, and not depending on product post-testing, he said.

Dr. Snape briefly outlined the format the final guide will take and presented a brief history of its development process. The guide is slightly behind schedule but will likely be ready in 2002, he concluded.

Discussion

Simon Taylor asked participants to discuss whether the detail of information supplied by the FDA and EMEA is appropriate to other countries, or if it creates a barrier to countries where access to basic products will save lives.

One participant said he would have liked to hear more about the regulatory environment in Japan. Dr. Farrugia apologized, saying that he was not well versed in the Japanese system, though it is a well-reputed structure. A participant

from Japan said that his country uses the same types of measures as the FDA and EMEA.

At the last global forum, there was more representation from treaters and patients, a participant said. However, what they think is irrelevant, he said, since governments still have ultimate regulatory authority and each makes decisions its own way.

Another participant cautioned against giving the message never to test finished product. She agreed that there are problems with post-production testing, but suggested that it is more important to explain the limitations and urge the development of more meaningful finished product tests. While she lauded the development of the regulatory guide, she urged participants to remember the importance of education around many issues.

Dr. Snape was asked how it would be possible for the guide to be so short, only 25 pages. He replied that the guide does not spend a lot of time describing the complexities of EU and U.S. regulations; but focuses instead on what they do that is suitable in other environments, and what can be substituted to ensure suitable assurances of quality and safety.

A participant from a developing country recalled that the guide started with the realization that developing countries do not have the resources to design regulatory processes themselves, and that following EMEA and FDA guidelines would result in a total lack of affordable products. Therefore, he asserted, the guide was intended to be a set of good minimum standards. If the guide does not meet those requirements, he said, there is not much advantage to publishing it.

Another participant suggested that two different documents are needed. The first, he said, should be an evidence-based mechanism that explains the results of doing without particular measures or processes, so each country can make informed choices and adapt the mechanism to the particular situation in a country.

Several participants agreed that the guide was the most important result of the last forum. One participant asked if there is a plan in place for its distribution, and stressed the importance of getting it out before the information in it becomes redundant. A representative of PPTA volunteered that organization's assistance in the distribution process.

It was suggested that in addition to the guide, it would be helpful to have a panel of experts who can provide practical information and advice.

Another participant recommended tying the guide to work being done by the WHO to lend it greater weight and credibility.

Most developing countries have little or no regulating authorities in place, a participant noted, even for other pharmaceuticals. The guide could be extremely valuable in evaluating products that have no established track record, he said, and looked forward to its release.

Session 7: Feedback and Next Steps

Because some participants had to leave early to start their journeys home, Dr. Peter Jones opened the final session by thanking WFH Executive Director Line Robillard and her staff for their terrific job organizing the forum. He thanked the audiovisual team for a nearly glitch-free meeting. He thanked Simon Taylor for his hard work, the speakers for their brevity and focus, and the delegates for their participation.

Brian O'Mahony explained that the feedback session is an opportunity to talk about safety and supply issues and future steps. He introduced members of the WFH Task Force on TSEs and gave the assurance that if there is a major development in the area the TSE Task Force will get the word out. The WFH intends to be more proactive and provide input when changes to regulatory practices are being considered, he stated.

Mr. O'Mahony noted that this is the second global forum and asked participants how it compared with the first. Should there be a third forum and if so, what format it should take?

A participant from industry said that this was his first forum and he found it very helpful and would like to see another.

Participants voted on the following question:

Should the WFH organize another global forum?

Yes	92%
No	8%

Montreal was chosen as the site for the first two fora because it is cost effective, WFH staff is there, and it has good lines of communications, Mr. O'Mahony explained. Participants then voted on the following question:

Should Montreal be the site of the next forum?

Yes	77%
No	23%

A forum member noted that the year 2003 is the 40th anniversary of the WFH and asked if there would be a celebration of sorts, such as a retrospective or forecast at an event that year. Mr. O'Mahony replied this is being planned.

Keeping the forum topical is important, Mr. Taylor said. He encouraged participants to send along ideas and issues that should be discussed.

It was suggested that time be spent on the issue of developing products that would be accessible in countries without much money. Mr. Taylor said he felt that there was quite a focus on developed world issues this time. Participants then voted on the following:

Was the balance between speakers and discussion about right?

Yes	60%
No	40%

Should we have more discussion and fewer presentations?

Yes	59%
No	41%

Mr. Taylor said he took these results to mean that the balance was not far off.

He explained that forum organizers made an effort to keep the event a day and a half long so that people could fit it into their schedules, particularly those in industry. No one disagreed with that thinking.

One participant commented that the voting mechanism was a valuable way to measure opinion, and said it was interesting to see how opinions changed during the meeting. She encouraged continuing this practice.

Another participant expressed disappointment at the low number of participants from European national hemophilia organizations.

The first forum involved plenary sessions and breakout sessions into smaller working groups, one participant recalled. Mr. Taylor explained this format was not adopted this time because everybody wanted to hear and participate in all discussions. At the first forum, it was difficult to report back from the working groups, he added. As well, the workshops varied in effectiveness depending on the level of discussion. There was some discussion on the merits of the two formats.

Another participant suggested that since the forum is made up of groups with different viewpoints, it might be beneficial for those groups to split off and then come back to a plenary session for lively debate.

Should we have workshops at the next forum?

Yes	58%
No	42%

The breakdown of participants was roughly 30 from industry, 20 clinicians, 20 hemophilia organization leaders, and 10 regulators. This was seen as a good number of participants that allowed for discussion among the various stakeholders. One of the dynamics that organizers wanted to maintain was a feeling of equality, a sense that participants are all peers. They were pleased to have more regulators than at the last forum.

A participant expressed support for keeping the forum about the same size because the nature of the discussions would change with a larger group.

It was good to hear other points of view, another said. "We are all used to talking to our own groups. Here, we hear views that we aren't usually exposed to." In the first forum, the group was broadly split between developed and developing countries on most issues.

There was a suggestion that more case studies be presented next time. People agreed that hearing "war stories" and practical examples was one clear benefit of the forum.

Mr. Taylor thanked participants for their thought-provoking input; the WFH has valuable perspectives and findings to take back, Mr. Taylor said. He asked if participants felt that too much or not enough time had been spent on vCJD.

A participant noted the heavy criticism on the issue of how and when batches of finished product can safely be released. It would be interesting to hear from an expert; he made a proposal to invite experts on batch release to provide an overview. He asked if the European regulatory system would be reviewed at a future forum, and suggested inviting someone from the EMEA secretariat.

Another participant said that it would have helped those who were affected by the shortage caused by Bayer problems to hear from the FDA. He also asked what will be revisited at Seville. Dr. Giangrande replied that there is one scheduled session focusing directly on the supply of recombinant products.

There was a call for a full discussion of the Bayer-related shortage problem, since there are a lot of lessons to be learned from what happened. Dr. Giangrande replied that the decision had been made to add extra symposia on supply issues for plasma and recombinants at the WFH congress.

Various groups are represented at the forum and the proper relationship between these groups is an issue, a participant said. The relationship varies from country to country. Lack of communication or too much collaboration can both be problems. In the U.S., there was a feeling that individuals and doctors had too much of a role. On the other hand, mistakes can be made due to a lack of communication. Bridge building between groups is essential, and each relationship is a balancing act.

Another participant responded that in Europe, patients are still beating on the door to get in. "We'd like the problem to be that of being too close."

Mr. O'Mahony agreed that national hemophilia organizations would benefit from examining their structure and their role.

He expressed his thanks to everyone for making the journey, and said the WFH will organize another forum for next year.

List of Participants

Nabil Ackad, Novo Nordisk Canada Inc., Canada
Fereydoun Ala, National Blood Service, U.K.
Tom Alloway, Canadian Hemophilia Society, Canada
Pantep Angchaisuksiri, Hemophilia Society of Thailand, Thailand
Inger Antonsson, Biovitrum AB, Sweden
Norhanim Asidin, Haemophilia Society of Malaysia, Malaysia
Mary Bauman, Bayer, U.S.A.
Alain Baumann, Baxter Bioscience, U.S.A.
Wolfgang Biering, Octapharma Pharmazeutika, Austria
Walter Brulez, Biotest Pharma GmbH, Germany
J. M. Bult, Plasma Protein Therapeutics Association, U.S.A.
Manel Canivell, Grupo Grifols S.A., Spain
Sharon Caris, Haemophilia Foundation of Australia, Australia
Larisa Cervenakova, The American Red Cross Holland Laboratory, U.S.A.
Joy Charley, Belize Hemophilia Society, Belize
Gordon Clarke, European Haemophilia Consortium, Northern Ireland
Sally O. Crudder, Centers for Disease Control and Prevention, U.S.A.
Luis Cruz, Aventis Behring LLC, U.S.A.
Francine Décary, Héma Québec, Canada
Mario Donoso Scroppo, Ministry of Health, Chile
John Edwards, Wyeth/Genetics Institute, U.S.A.
Magdy El Ekiaby, Egyptian Society of Hemophilia, Egypt
Bruce Evatt, Centers for Disease Control and Prevention & World Federation of Hemophilia, U.S.A.
Theo Evers, European Plasma Fractionation Association, the Netherlands
Bruce Ewenstein, National Hemophilia Foundation, U.S.A.
Armand Famiglietti, Alpha Therapeutic, U.S.A.
Steve Farrell, Aventis Behring LLC, U.S.A.
Albert Farrugia, Therapeutic Goods Administration and World Federation of Hemophilia, Australia
Denis Flanaghan, Alpha Therapeutic Corporation, U.S.A.
Neil Frick, National Hemophilia Foundation, U.S.A.
Peter Ganz, Health Canada, Health Products and Food Branch, Canada
Cesar Garrido, Associacion Venezolana para Hemofilia, Venezuela
Paul Giangrande, Oxford Haemophilia Centre & World Federation of Hemophilia, U.K.
Marc Greenwood, Bio Products Laboratory, U.K.
Stefano Guazzini, Kedrion, Italy
Manfred Haase, Paul Ehrlich Institut and the European Agency for the Evaluation of Medicinal Products (EMEA), Germany
Mathias Haun, Canadian Blood Services, Canada
Cheryl Hayden, National Hemophilia Foundation, U.S.A.
W. Keith Hoots, University of Texas Houston Health Science Center, U.S.A.
Ching-Li Hu, Shanghai Second Medical University, China
Heather Hume, Canadian Blood Services, Canada
Peter Jones, World Federation of Hemophilia, U.K.
Carol Kasper, Los Angeles Orthopaedic Hospital, U.S.A.
Howard Kelly, Baxter, U.S.A.
Timothy Keutzer, Wyeth/Genetics Institute, U.S.A.
Stephen Kinsman, Magnus Consultants, Canada
James Kreppner, Canadian Hemophilia Society, Canada
Daniel Lapointe, Canadian Hemophilia Society, Canada
Koon Hung Luke, Children's Hospital of Eastern Ontario, Canada
Jane Martin, Bio Products Laboratory, U.K.

List of Participants continued...

Laurel Mc Donnell, NuFactor and FFF Enterprises, U.S.A.
Rene McRogers, Bayer, U.S.A.
Judi Miller, Octapharma Produtos Farmaceuticios, Portugal
Elizabeth Myles, World Federation of Hemophilia, Canada
Anthony Nagle, Bayer, U.S.A.
Masako Nakamura, Wyeth/Genetics Institute, U.S.A.
Maria Foshi, Nivia Unidade de Hemofilia - Hospital Brigadeiro, Brazil
Brian O'Mahony, World Federation of Hemophilia, Ireland
Ana Padilla, World Health Organization, Switzerland
David Page, Canadian Hemophilia Society & World Federation of Hemophilia, Canada
Andy Pickett, IPSEN Limited, U.K.
Glenn Pierce, National Hemophilia Foundation, U.S.A.
Dominique Pifat, Bayer
Man-Chiu Poon, Southern Alberta Hemophilia Clinic, Canada
Peter Pustoslemsek, Biotest Pharma GmbH, Germany
J. Wesley Rees, Canadian Blood Services, Canada
Bruce Ritchie, Association of Hemophilia Clinic Directors, Canada
Line Robillard, World Federation of Hemophilia, Canada
Wolfgang Schramm, Ludwig-Maximilian University Hemophilia Centre, Germany
Sam Schulman, Karolinska Hospital & World Federation of Hemophilia, Sweden
Dorothy Scott, Food and Drug Administration, U.S.A.
Claudio Siqueira, Biotest Pharma GmbH, Germany
Mark Skinner, National Hemophilia Foundation, U.S.A.
Terry Snape, Pharmaceutical Consultant, U.K.
Alok Srivastava, Christian Medical College Hospital, India
Jean St-Louis, Maisonneuve & Ste-Justine Hopitals, Canada
Bob Summers, American Red Cross, U.S.A.
Hideaki Suzuki, Ministry of Health, Japan
Simon Taylor, The Haemophilia Society, U.K.
Aliakbar Tchupan, Iranian Hemophilia Society, Iran
Geoffrey Thomas, Baxter Corporation, Canada
H. Marijkeala van den Berg, Van Creveld Clinic - National Hemophilia Center, Germany
Ashok Verma, Hemophilia Federation (India) & WFH, India
Peter Vichi, IPSEN Inc., U.S.A.
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Frantisek Vondryska, Czech Haemophilia Society, Czech Republic
Chaim Waissman, ALEH - Israeli Hemophilia Organization, Israel
Charles Waller, Plasma Protein Therapeutics Association Europe, Belgium
Xuefeng Wang, Shanghai Haematology Research Center, China
José Willemse, Netherlands Haemophilia Society, The Netherlands
Jun Xu, Shanghai RAAS Blood Products Co. Ltd., China
Kin Yeung, American Red Cross, U.S.A.
Yuri Zhulyov, Russian Hemophilia Society, Russia