Paul-Ehrlich-Institut
Bundesamt für Sera und Impfstoffe
Federal Agency for Sera and Vaccines

WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices

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Paul-Ehrlich-Institut (PEI)

WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices

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A World Health Organization Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices

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Preface

Blood is not only – as the German poet Goethe said - a very special fluid, but blood and several derivatives made from blood are invaluable and often life-saving medicines. Many modern state-of-the-art therapeutic interventions would not have been developed without the option to give blood or blood products to the patients. However, we had to learn that these indispensable medicines may also bring about detrimental consequences. The epidemic with numerous transmissions of dangerous viruses such as HIV by blood transfusions and plasma derivatives in the early 80ies of last century can be regarded one of the worst disasters in the recent history of medicine. Much has been done in the past decades to increase the safety of blood and blood products, and a very high standard could be achieved in the developed countries.

The Paul-Ehrlich-Institute (PEI) is the German Federal Authority responsible for the regulatory control of blood products since 1994. The PEI works in several ways to ensure the safety of medicinal products derived from blood: Licensing of products (marketing authorization), official batch release including laboratory testing and review of the documentation of source materials and manufacture, inspections in cooperation with regional authorities, haemovigilance and pharmacovigilance with the capacity to impose corrective measures, contribution to the drafting important legal and guidance documents by official bodies and committees, and active experimental scientific research. Of crucial importance for the prevention of the transmission of pathogens by blood products are sensitive and reliable test methods to detect infection markers. Importantly, the PEI has also long-standing experience with the regulatory control of in vitro diagnostic devices and performs intensive laboratory research in this field. The continuous independent assessment of the test kits by the PEI has been an important driving force towards optimizing the tests and helped the industry to improve their products. It is of particular value to have the regulatory responsibility, and the laboratory capacity to perform competent experimental assessment and research within the same institute.

It is a priority objective of the WHO to establish functioning and safe blood systems throughout the globe. The PEI is proud to be assigned as a WHO Collaborating Centre, and determined to do its best to help pursue this great goal.

Rainer Seitz
November 2006

Part I –Terms of Reference as designated in June 2005

General Framework

The overall objective of the proposed collaboration is to support WHO in strengthening the technical and regulatory capacity of regulatory authorities worldwide for the evaluation and control of blood products and in vitro diagnostic devices. The WHO International Conference on Drug Regulatory Authorities (ICDRA) held in Madrid in 2004 requested WHO to contribute to the advancement of technical expertise of regulatory authorities aiming at the development of a global network of regulatory authorities for blood and blood products and in vitro diagnostic devices. The Paul-Ehrlich-Institut (PEI) considers this request of high relevance in public health and offers WHO the expertise and cooperation in this area of work.

A) Support to WHO in the organization of training courses and meetings covering the following fields of activity

a) GMP inspections of blood establishments and plasma fractionation facilities.

b) Review of production protocols and laboratory control of batches, including testing of viral markers.

c) Regulatory control systems for blood components and plasma derivatives, covering:

   i) assessment of quality

   ii) administrative procedures.

d) In vitro diagnostic devices:

   i) validation of assays

   ii) evaluation of performance of IVDs

   iii) control and batch release of IVDs

   iv) evaluation of viral safety of blood derived products:
   plasma pool testing by nucleic acid amplification techniques (NAT)
   plasma pool testing by serological methods
   safety evaluation of plasma derivatives

   v) evaluation of pathogen inactivation/removal procedures.

B) Laboratory studies and standardization exercises

a) Active contribution in design and organization of collaborative studies in order to establish international standard preparations and reference panels.

b) Experimental research, particularly into the development of improved test methods.

c) Quality control of blood and plasma derived medicinal products and in vitro diagnostic devices.

C) Contributing to the development of guidelines and recommendations

a) Sharing longstanding and broad experience due to involvement in several national and international committees, including the EMEA working parties and expert groups of the European Pharmacopoeia

b) Active contribution to keeping updated WHO guidance documents (e.g. Technical Report Series, No. 840).

Part II – Implementation of the work plan in relation to the terms of reference

1. Blood Regulators Network (BRN)

The 11th International Conference on Drug Regulatory Authorities (ICDRA, Madrid, Spain, 16 – 19 February 2004) recommended the formation of a global network of regulatory authorities for blood and blood products. The request was formally recognized at the annual meeting of the WHO Expert Committee on Biological Standardization (ECBS) in Geneva, Switzerland in 2004 and affirmed in 2005.

A concept paper of the terms of reference for the “peer regulators group” was drafted by Professor Rainer Seitz of the Paul-Ehrlich-Institut (PEI)[1] in June 2005. The concept was presented by Professor Johannes Löwer (the President of PEI) and discussed at the ECBS meeting in October 2005. Terms of reference of the now so-called Blood Regulators Network (BRN, as agreed at the ECBS meeting in 2005) were finalized in June 2006. Initially, the network will be comprised of six regulatory authorities (referred to as "Members") which have responsibility for the regulation of blood, blood products and related in vitro diagnostic devices (IVDs) and the necessary expertise and capacity to address emerging public health challenges. Members are (in alphabetical order of countries): Therapeutic Goods Administration (TGA), Australia; Health Canada, Canada; Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), France; Paul-Ehrlich-Institut, Germany; Food and Drug Administration (FDA), U.S.A., and Swissmedic, Switzerland. Representative of PEI will be Professor Seitz. The Network shall report to ECBS. WHO/HTP/PSM/QSD (Health Technologies and Pharmaceuticals/ Medicines Policies and Standards/ Quality and Safety of Plasma Derivatives) will provide Secretariat support to the activities of the network and act as a central repository of information and documentation.

Main objectives will be to:

- “identify issues
- share expertise and information
- promote convergence of regulatory policy and
- propose solutions to specific issues, especially emerging public health challenges”.

[1] PEI staff members are mentioned by name. They are listed at the end of the report.

The Network shall focus on the following areas with a particular emphasis on reacting quickly and flexibly to critical situations:

- "scientific assessment of current and emerging threats to the safety and availability of blood and blood products;
- scientific assessment of the impact (i.e. potential benefits and drawbacks) of new technologies in the field of blood and blood products;
- exploration of opportunities among regulatory authorities to cooperatively address emerging public health challenges; and
- exploration of opportunities for regulatory collaboration/harmonization, particularly in response to emerging public health challenges (such as, for example, actions to prevent transmission of emerging agents in blood products or tools for removing these agents).".

2. PEI contributions to the WHO Expert Committee of Biological Standardization (ECBS) and related meetings and consultations

2.1 56th ECBS Meeting, Geneva, Switzerland, 24 – 28 October 2005

PEI activities as a WHO Collaborating Centre are closely linked to ECBS. Professor Löwer as a member of the Expert Panel chaired the blood products session of the 56th meeting in October 2005. He also reported the plenary about the Blood Regulators Network project. The network was asserted formally by the Committee at the end of the meeting.

2.2 Technical Workshop on Stability of Reference Materials for Biological Medicines, Geneva, Switzerland, 28 – 29 November 2005

The Expert Committee recommended to WHO in 2004 to start working on the prediction and monitoring of the stability of biologicals. Thereupon a working group about reference material stability was established and endorsed by ECBS in 2005. The first meeting took place at WHO headquarters in November 2005. It was chaired by Dr Jin-Ho Shin WHO/FCH/IVB/QSD (Family and Community Health/ Immunization, Vaccines and Biologicals/ Quality and Safety of Biologicals).

The group consists of regulatory authority representatives (like China, Germany, Japan, Thailand, UK), representatives of industry (EDMA, European Diagnostic Manufacturers Association) and EDQM (European Directorate for the Quality of Medicines). The PEI Collaborating Centre is represented by Dr Sigrid Nick.

The main scope is the development of a WHO Guideline. This aim was discussed controversially at the first meeting because a guideline (EN 13640:2002; Stability testing of in vitro diagnostic reagents) already exists and industry does not see any further need for actions. There is some concern that WHO would complicate the matter. However, a draft concept paper was written by Dr John Diment, which states that the working group shall design and carry out stability studies “to meet agreed requirements set at the initial review with appropriate experts in the class of material. These requirements may include, for example, those of the US Food and Drug Administration (USA FDA), the Japanese Ministry of Health and Welfare (MHW) and the European Directive 98/79/EC (IVD Directive), ISO, CEN, Pharmacopoeia and other standards as agreed for the appropriate class of material”.

2.3 Consultation on Transmissible Spongiform Encephalopathies (TSEs), Geneva, Switzerland, 14 – 16 September 2005

The consultation was held to revise the WHO Guidelines on Transmissible Spongiform Encephalopathies (TSEs) in relation to Biological and Pharmaceutical Products of 2003. The tissue infectivity tables were updated and recommendations provided in order to prevent potential transmission of vCJD through human blood and blood products, as well as through medicinal products prepared with bovine derived materials. The Guideline was adopted by ECBS in October 2005. Professor Löwer joined the meeting as PEI expert for TSEs. The Guideline is provided on the WHO/PSM/QSD Web site:
http://www.who.int/bloodproducts/tse/WHO%20TSE%20Guidelines%20FINAL-22%20JuneupdatedNL.pdf

3. Support to WHO in the organization of training courses and meetings in the field of regulatory control systems for blood components and plasma derivatives and in vitro diagnostic devices (IVD), covering assessment of quality and administrative procedures

3.1 WHO Regional Office for the Eastern Mediterranean (EMRO) Consultation for Quality Assurance and Safety of Plasma and Plasma Derivatives in Cairo, Egypt, 31 January – 3 February 2005

Professor Löwer joined the WHO/ EMRO Consultation as facilitator. 26 participants from national medicines regulatory authorities, national blood programmes and plasma fractionators in ten WHO Eastern Mediterranean Regional countries (Bahrain, Egypt, Iran, Jordan, Morocco, Oman, Saudi Arabia, Sudan, Tunisia, and United Arab Emirates) participated in the workshop. The criteria for selecting the countries invited were as follows: countries with plasma fractionation activities; countries that are or will be involved in plasma contract fractionation programmes in the near future and countries importing products whose medicines regulatory authorities had expressed interest in participating in the workshop before.

Main requests from Member States related to regulatory and scientific challenges derived from the use of human plasma as the starting material for the preparation of plasma derivatives.

Professor Löwer gave detailed presentations about the quality assurance system of blood screening tests at PEI; the characteristics, advantages and limits of viral inactivation and removal procedures; the quality and safety of blood products with regard to viral safety testing by nucleic acid technology (NAT), including batch release. He also gave an overview of the recommendations of the International Conferences of Drug Regulatory Authorities (ICDRA) of 1999, 2002 and 2004 with respect to blood safety issues.

Furthermore Professor Löwer chaired a working group which summarized the main issues and needs of the participating countries. As a main outcome the reactivation of the network of national regulatory authorities (NRAs) within the Region was agreed. A steering committee was formed to promote harmonization of regulatory policies for the evaluation and control of medicinal products derived from human blood and plasma. It is comprised of representatives from NRAs of Bahrain, Egypt, Iran and Tunisia. The complete recommendations and outcomes are available on the WHO/ QSD Web site:
http://www.who.int/bloodproducts/publications/cairo2005_Recomendations.pdf

3.2 ICDRA Meeting 2006, Seoul, Republic of Korea, 3 – 6 April 2006

Prior to the ICDRA meeting a so-called Pre-ICDRA meeting “Improving world health through regulation of biological medicines” was held for the first time (1 – 2 April). This meeting about the regulation of biological medicines, which are getting more awareness all over the world, was very successful and shall be implemented on a regular basis in connection with the ICDRA meeting.

Professor Löwer joined both the Pre-ICDRA as well as the ICDRA Meeting as representative of PEI.

3.2.1 Pre-ICDRA Meeting

- At the Pre-ICDRA session about biological products he gave an overview of the regulatory challenges of gene therapies as products at the cutting edge of biologicals development.
- In the session about blood products he talked about safety assessment and regulatory issues in blood products, including the quality of in vitro diagnostic devices.

3.2.2 ICDRA Meeting

ICDRA workshop “Regulation of Blood and Blood products: Global Challenges”

As chairman of the workshop Professor Löwer summarized the recommendations of the Pre-ICDRA as follows:

Safety assessment and regulatory issues:

- Three principal complementary approaches can be adopted to control potential viral contamination of biologicals:
  - — selecting and testing source material for the absence of viruses,
  - — testing the capacity of the production processes to remove or inactivate viruses,
  - — and testing the product at appropriate stages of production for freedom from contaminating viruses.
- Screening tests have to be appropriately controlled through independent evaluations performed by regulators.

Rapid responses to emerging agents affecting blood products:

- functioning infrastructure needed:
  - effective surveillance system
  - capacity for epidemiological investigations
  - laboratory infrastructure
  - risk assessment tools
  - communication mechanisms
  - control activities
- appropriate risk communication
- cooperative interaction between governments, blood organizations and device manufacturers.

Role of post-marketing surveillance of blood products:

- pharmacovigilance and haemovigilance
- well structured notification system
- well standardized and operating traceability system
- two direction traceability:

  Recipient => donor
  Donor => recipient.

Risk-based approach to blood products regulation in Australia and New Zealand:

- joint regulatory authority will be effective from January 2007
- not only plasma derivatives but also blood components will be regulated by this authority.

Regional networks of regulators for blood products: needs and expectations:

- WHO workshops in Havana 2001 and Buenos Aires 2004
- Pan-American network for drug regulations harmonization (PANDRH), 1999
- blood regional technical group: GMP, inspections, pharmacovigilance.

Session "Emerging Diseases and Crisis Management: Regulatory Challenges"

Professor Löwer informed the plenary about the emerging threats to the safety and availability of blood and blood products in Germany, focused on approaches to control potential contamination of biologicals including blood products by viruses (HIV, hepatitis, West Nile virus, influenza virus, chikungunya virus) or vCJD agent.

4. Contribution in design and organization of collaborative studies in order to establish WHO International Biological Measurement Standards (IS) and Reference Panels

4.1 HBV WHO Subtype Panel

Project leader: Dr Micha Nübling

During the WHO Consultation on Global Measurement Standards and their use in the in vitro Biological Diagnostic Field in June 2004 (joined by Dr Nick, PEI) concern was raised that commercial HBsAg and HBV NAT test kits could be less sensitive for HBV genotypes other than A2. Different HBV genotypes are found more frequently in developing countries. It was agreed that the subject should be investigated further. During the ECBS meeting in October 2005 the project of establishment a WHO International Standard Panel of HBV geno- and subtypes was assigned a high priority. Currently Dr Nübling is collecting around 15 different geno- /subtype samples in adequate amounts from different regions of the world. Yet, no provider for subtype F could be found. The efforts are continuing.

4.2 Anti-HBc WHO International Standard

Project leader: Dr Heiner Scheiblauer

Anti-HBc is an important marker for the detection of chronic HBV infection. In order to improve blood safety with regard to HBV, screening for anti-HBc antibodies complementary to HBsAg testing has been introduced at a continuously increasing rate around the world. To be able to calibrate test systems, laboratories ask for a primary standard. So far, the current PEI anti-HBc standard (no 82, serum, 100 PEI U/ml) has been used worldwide and anti-HBc PEI units have been introduced in many assays.

At the meeting in October 2005 the ECBS endorsed the project to establish a WHO International anti-HBc Standard as proposed by PEI.

Up to now the following investigations were performed: the PEI anti-HBc standard no 82 and plasma material provided by NIBSC (NIBSC no 95/522) were tested in 14 different CE-marked anti-HBc assays.

A third sample was included in this study which originates from an “anti-HBc only” HBV positive blood donor who had transmitted HBV infection via labile blood

components. The undiluted plasma reacted low positive and might be used as a “benchmark control” for anti-HBc screening assays.

The advantages and disadvantages of the respective materials need to be discussed by the respective experts of the WHO Collaborating Centres and/ or the WHO Working Group on IVD Reference Materials. A decision needs to be made which candidate material(s) appear(s) suitable and shall be put forward to a WHO collaborative study.

4.3 Reference Panel of anti-HCV monospecific samples

Dr Nico Lely of the former WHO Collaborating Centre Sanquin performed a feasibility study for the investigation of anti-HCV monospecific samples in 2004. PEI (Dr Nick) participated in the study. After the end of the collaboration of Sanquin with WHO, Dr Nick of PEI was asked to continue the study. At the ECBS meeting in 2005 the study was regarded as being of high priority. Neither feasibility study report, nor samples were provided to PEI yet.

5. Contribution in WHO collaborative studies organized by other WHO Collaborating Centres

5.1 Participation in WHO International Standard collaborative studies of blood products

The PEI laboratory of section 7/3, “Batch Release of Blood Products, Albumin, Logistic” took part in four collaborative studies to assign potency values to proposed WHO International Standard (IS) materials. The proposed candidate IS materials were processed according to guidelines for the production of WHO IS at NIBSC. These WHO IS are now / will soon be available for the calibration of secondary standards as well as commercial reference plasmas in order to improve inter-laboratory harmonization worldwide.

CS: WHO 1st International Standard for Blood Coagulation Factor XIII Plasma (NIBSC code 02/206) (WHO/BS/04.1994 Rev.1)

Date: 07/2005 – 09/2005
Method: ELISA

CS: WHO 1st International Standard Factor V Plasma (NIBSC code 03/116) (WHO/BS/05.2007)

Date: 10/2004 – 08/2005
Method: FV - clotting test

CS 278: WHO 1st International Standard for Blood Coagulation Factor XI, Plasma, Human (NIBSC code 04/102) (WHO/BS/05.2017)

Date: 04/2005 – 08/2005
Method: FXI - clotting test

To be submitted to ECBS 2006:

Collaborative Study (CS):
1st International (WHO) Standard for Alpha-1-Antithrypsin (AAT) (NIBSC code 05/162) (WHO/BS/06.2044)

Date: 02/2006 – 06/2006
Method: Active site titration of Trypsin and Alpha-1-Antitrypsin

5.2 Current activities in the standardization of blood typing reagents

Two new WHO International Standards for blood typing, a monoclonal anti-A and a monoclonal anti-B standard were adopted by ECBS in 2005. Dr Susan Thorpe of NIBSC had organized the collaborative study. However, at the ECBS meeting in October 2005 participants asked for additional data, especially with modern methods like automatic systems or gel filtration assays (tube testing had been performed for the international study). Dr Heidi Soboll at PEI is currently working with the standards to raise additional data. The data will be forwarded to NIBSC in order to include them in the product information.

6. Funding by WHO

30.000 USD were provided by WHO/HQ/PSM/QSD end of 2005 to sustain the PEI CC project of the establishment of a HBV subtype panel (see 4.1). Most of the money will be needed for the provision of samples from different laboratories around the world and for the preparation/ purification of the samples by Professor W. Gerlich, University of Gießen, Germany.

7. Contribution to the development of guidelines and recommendations

PEI experts were involved in the development of new WHO Guidelines:

- WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies (Consultation at WHO/HQ in September 2005, see point 2.3).
- WHO Recommendations for the Production, Control and Regulation of Human Plasma for Fractionation (adopted by ECBS 2005). The revised draft was discussed and finalized during the ECBS meeting in 2005 in the session of blood products, which was chaired by Professor Löwer.

8. Offer of training courses for assessors working in regulatory authorities

8.1 Trainings at PEI WHO Collaborating Centre planned for 2006

Two employees of the Sudanese National Drug Quality Control Laboratory, which is a part of the Sudanese Ministry of Health, intend to visit the PEI CC for training in October / November 2006. The training was proposed by Dr Ana Padilla, WHO headquarters.

They will stay for six weeks each. Besides the units/sections of the Collaborating Centre, other units of PEI will be visited as well.

One trainee (A) intends to join the PEI CC

- Section 1/3: Microbial Safety and Parasitology (head: Dr Thomas Montag-Lessing);
- Section 7/3: Batch Release, Blood Products, Albumin, Logistics (head: Dr Uwe Unkelbach).

The other trainee (B) intends to join the PEI CC

- Section 2/5: Viral Safety (head: Dr Johannes Blümel);
- Section 3/2: Monoclonal and Polyclonal Antibodies (head: Dr Christian Schneider);
- Department PEI-IVD: Testing Laboratory for IVD (head: Dr Sigrid Nick);
- Unit S2: Vigilance of in vitro Diagnostics (head: Dr Markus Funk).

Both trainees are expected to work at PEI WHO Collaborating Centre sections/ units for 30 days each. They will be asked to fill in a questionnaire at the end of the training for the evaluation of the training quality.

Table 1

Training at the PEI WHO Collaborating Centre in 2006

	Duration [d]	Trainee
PEI WHO Collaborating Centre:		
Section 1/3 **Microbial Safety and Parasitology**	**10**	**A**
Section 2/5 **Viral Safety**	**2**	**B**
Section 3/2 **Monoclonal and Polyclonal Antibodies**	**10**	**B**
Section 7/3 **Batch Release, Blood Products, Albumin, Logistics**	**5**	**A**
Department PEI-IVD **Testing Laboratory for IVD**	**5**	**B**
Unit S2 **Vigilance of in vitro Diagnostics**	**3**	**B**
Additional sections/ units of PEI:		
Sections 1/1 and 1/2 **Bacterial Vaccines I and II**	**5**	**A**
Section 2/1 **Viral Vaccines**	**10**	**B**
Division 5 **Allergology**	**5**	**A**
Unit S1 **Pharmacovigilance**	**5**	**A**
Total days each	**30**	

8.2 Other trainings for international regulators at PEI WHO Collaborating Centre sections/ units in 2006

Four more trainees from:

- Turkey (Ministry of Health, one week in Department PEI-IVD, Unit S2, IVD Vigilance and Section 7/3, Batch Release of Blood Products),
- Egypt (Cairo University, three months in Department PEI-IVD),
- China (Biological products Control Laboratory, Shanghai Institute for Drug Control (SCID), Shanghai, P.R. China, four weeks in Department PEI-IVD and Section 7/3, Batch Release of Blood Products) and
- Japan (National Institute of Infectious Diseases (NIID), Tokyo, four months in Section 1/3, Microbial Safety)

visited PEI or intend to come for training to WHO CC associated sections in 2006.

8.3 One day visitors of the PEI WHO Collaborating Centre

A colleague of the Australian Health Government and a group of five persons of the Chinese Shenzhen Municipal Institute for Drug Control visited parts of the CC in 2006 hitherto and were informed about the PEI activities including WHO collaboration.

9. Secondments

Dr Gabriele Unger (PEI Testing Laboratory for IVD at that time) was delegated from PEI to WHO headquarters in Geneva, Switzerland (HTP/EHT/QSD), in order to support WHO activities in the field of in vitro diagnostic devices. The secondment was planned for a period of six months. It was prolonged to 15 months, from July 2004 until end of October 2005.

Dr Michael Chudy (PEI Testing Laboratory for IVD) is currently seconded to WHO headquarters (HTP/PSM/QSD) to support Dr Ana Padilla's efforts for improvement of regulation systems of in vitro diagnostic devices. He started working on 4 September 2006 and will stay at WHO for eleven months.

10. Other WHO Meetings, related to PEI CC activities

10.1 WHO /ISBT cooperation

In 2005 the International Society of Blood Transfusion (ISBT) established a TTID (transfusion transmitted infectious diseases) working group to found a world-wide repository for rare and interesting human samples characterized by viral markers. The group is chaired by Professor W.K. Roth, GFE (Gesellschaft für Forschung und Entwicklung), Frankfurt/Main, Germany. WHO is represented by Dr Padilla and Dr Nübling is another institutional member as representative of PEI. The final (working) structure of the repository has still to be worked out, discussions are ongoing. The last meetings of the working group took place in Washington, USA in March 2006 and in Cape-Town, South Africa, on 2 – 3 September 2006.

10.2 WHO/ISTH (International Society on Thrombosis and Haemostasis) Liaison Group Meeting, Oslo, Norway, 28 June 2006

The meeting of the WHO/ISTH Liaison Group took place in Oslo as part of the ISTH SSC (Standardisation and Scientific Committee) Meetings. The WHO is represented in the Liaison Group by Dr Padilla. Further members are an ISTH liaison officer, the chairperson of SSC, a member of the ISTH Council, and WHO CC related to blood: NIBSC, FDA CBER, Sanquin (of which the status as WHO CC ended), and the PEI, for which Professor Seitz attended the meeting.

The terms of reference of the Liaison Group were discussed:

- To ensure the timely flow of biological standards related to haemostasis and thrombosis through a sound “peer review process” in and between organizations through to final establishment by ECBS.
- To advise the ECBS of the priorities of various standards to be developed, replaced or discontinued as well as on new methodologies, taking into account the needs in the various WHO regions.
- To discuss regular information on the development and assessment of such standards.
- To discuss and recommend as appropriate to ISTH/SSC and WHO/ECBS issues related to the preparation/ assessment/ publication of biological standards in the field of haemostasis and thrombosis as and when deemed appropriate by the group.

Further topics were the cooperation with ISBT in the field of platelet antibodies, WHO thromboplastin guidelines (the International Standard for thromboplastin will be moved from Sanquin to NIBSC), streptokinase potency assay, proposals by NIBSC for further standardization activities and submissions to ECBS. Professor Seitz, who is also ISTH liaison person to the European Medicines Agency (EMEA) reported about an EMEA workshop about Factor VIII inhibitors in haemophilia treatment in London from 28 February to 2 March 2006.

10.3 WHO Informal Consultation on Specifications and Validation of HIV/ AIDS Diagnostic Technologies, WHO/HQ, Geneva, Switzerland, 12 – 14 September 2005

Secretary of the meeting was Dr Gaby Vercauteren, WHO/HTP/EHT/DIL (Health Technologies and Pharmaceuticals/ Essential Health Technologies/ Diagnostics and Laboratory Technology). Participants came from national regulatory authorities as well as from UNICEF, the Clinton and the Gates Foundation. PEI was represented by Dr Markus Funk as head of the German Competent Authority for in vitro diagnostic Devices (PEI Unit Vigilance of in vitro Diagnostics). Licensing procedures in different countries were discussed, validation schemes and performance evaluation data reviewed in order to set common standards and criteria (for NAT assays as an example). Subgroups discussed about specification and minimum criteria for HIV tests, specifications and minimum criteria for CD4 technologies and specifications for virological testing in general. Rapid assays were in the main focus of the meeting, as developing countries are often using them for screening. Screening schemes for the clarification of initial reactive samples shall be developed to reduce the costs to a minimum.

10.4 6th General Annual Meeting of the Global Collaboration for Blood Safety (GCBS), Bangkok, Thailand, 16 – 18 November 2005

The GCBS annual meeting was attended by Dr Uwe Unkelbach. Dr Neelam Dhingra from WHO/HTP/EHT/BTS (Health Technologies and Pharmaceuticals/ Essential Health Technologies/ Blood Transfusion Safety) is the Secretary of the group. Experiences from blood transfusion settings around the world were shared with the plenary. Participants of the WHO Regional Office for South-East Asia (SEARO) focussed on malaria assays, representatives of the Ministry of Health of Thailand presented a working group for “disaster preparedness” that was founded after the Tsunami in 2004.

Dr Unkelbach did not give an official presentation, but many parties showed great interest in PEI batch release procedures.

The use of rapid tests was discussed as well. Some participants considered them to be equivalent to screening tests, while others, including the PEI, are concerned about the insufficient performance of such tests in general (with some exceptions). Finally, a positive declaration in the recommendations could be prevented.

The latter point shows the possibility of discrepant discussions about overlapping subjects of different WHO areas, and the importance of the role of CC such as the PEI in order to avoid contradictory actions and declarations.

Comparative evaluation of data on screening and rapid assays for blood donation testing would be a good basis for sound recommendations. Such data are hardly available. PEI is probably one of the most experienced institutions in the field and overlooks comprehensive data.

With regard to the annual meeting in 2006, PEI CC section Microbial Safety and Parasitology (head: Dr Montag-Lessing) intends to provide appropriate data following the GCBS recommendations 2005, point 10:
“GCBS participants recommended that the participating organizations promote the collection and sharing of data on the feasibility and utility in various settings of candidate strategies for:

- control of bacterial contamination in blood components …”.

The data shall be shared with interested parties in WHO.

11. Other (non- WHO) meetings and workshops, related to WHO and PEI CC activities

11.1 International Symposium on International Harmonization on Biopharmaceuticals, Seoul, Republic of Korea, 28 – 29 Oct 2004

Dr Johannes Blümel of the Viral Safety section of PEI attended the meeting organized by the Korean Food and Drug Administration (KFDA). The conference addressed the quality of various classes of medicinal products such as blood products, vaccines, biotechnological products and advanced therapies. KFDA was interested in the approaches of safety evaluation in different regions (USA, Europe, etc.).

Dr Blümel informed about the PEI activities concerning “Viral Safety Evaluation/ Validation of Biotechnology and Biological Products”.

11.2 Meeting on Development of Harmonization of QA Systems for Blood Products in Asian Countries, Bangkok, Thailand, 31 Oct – 2 Nov 2004

The Thai Ministry of Public Health, Department of Medical Sciences invited participants from six Asian countries (India, Indonesia, Japan, Republic of Korea, Malaysia, and Thailand) as well as facilitators from WHO (Dr Ana Padilla), USA (CBER) and the Paul-Ehrlich-Institut.
Dr Gerd Werner and Dr Johannes Dodt attended for PEI. The expected outcome was the initiation of an Asian regulatory network as requested by Member States at the ICDRA meeting 2004.

Dr Werner also attended as a representative of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and talked about the “Impact of GMP Regulations in Blood Products Safety”.

Dr Dodt gave an overview of the “Quality and Safety of Blood Products: Batch Release Harmonization” activities of PEI in Germany and as a member of the European Network of Official Medicines Control Laboratories (OMCL).

11.3 IPFA/PEI NAT Workshops on “Surveillance and Screening of Blood Borne Pathogens”

Together with the International Plasma Fractionation Association (IPFA) PEI is organizing annual scientific meetings, primarily on the topics of application of nucleic acid amplification tests (NAT) and other measures to increase blood safety. Among the different topics of the congress the issues of standardization of both approaches as well as assays are always represented. This meeting is now well-established and attracts around 150 - 200 attendees. The programme committee designing the contents of the congress and selecting speakers is chaired by a PEI representative, and various talks are regularly given by scientists from the PEI. In 2005 the meeting took place at the FDA in Washington, USA, the 2006 meeting was hosted by the Swiss authority Swissmedic in Berne.

12. Planned activities with participation of the PEI WHO Collaborating Centre

12.1 Workshop of the WHO Regional Office for the Eastern Mediterranean (EMRO) on Good Manufacturing Practice (GMP)

A GMP workshop is planned by WHO/EMRO in February / March 2007. PEI staff member(s) of Section 7/5, Inspections, shall participate in the workshop as facilitator(s). No programme is available yet.

12.2 German Presidency of the European Council in 2007

The PEI had been involved in the organization of an expert meeting during the German EU presidency 1999 in Wildbad Kreuth, Germany entitled: “Blood Safety in the European Community: An Initiative for Optimal Use”. The chair of the meeting, Professor Wolfgang Schramm, University of Munich, Germany, is planning a continuation of the initiative. A second meeting in Wildbad Kreuth in 2007, under the sponsorship of the University of Munich and the EU Commission shall take place. He again invited the German Ministry of Health and the PEI to join the organization committee. On occasion of the German Presidency in 2007, the PEI Collaborating Centre is currently exploring the possibilities of adequate contributions.

Current list of professional staff of the WHO Collaborating Centre

- Professor Rainer Seitz (head of the Collaborating Centre; head of PEI division 7, Haematology/ Transfusion Medicine)
- Professor Johannes Löwer, President of the Paul-Ehrlich-Institut

In alphabetical order:

- Dr Johannes Blümel (head of PEI section 2/5, Viral Safety)
- Dr Michael Chudy (current secondment to WHO/HQ/PSM/QSD; PEI section 2/4, Molecular Pathology)
- Dr Johannes Dodt (head of PEI section 7/2, Clotting Factors II)
- Dr Markus Funk (head of PEI unit S/2, Vigilance of in vitro Diagnostics)
- Dr Margarethe Heiden (head of PEI section 7/4, Transfusion Medicine)
- Dr Anneliese Hilger (head of PEI section 7/1, Clotting Factors I)
- Dr Thomas Montag-Lessing (head of PEI section 1/3, Microbial Safety and Parasitology)
- Dr Sigrid Nick (head of PEI Testing Laboratory for IVD)
- Dr Micha Nübling (project leader HBV Geno-/ Subtypes International Standard Panel; head of PEI section 2/4, Molecular Pathology)
- Dr Heiner Scheiblauer (project leader Anti-HBc International Standard; PEI Testing Laboratory for IVD)
- Dr Christian Schneider (head of PEI section 3/2, Monoclonal and Polyclonal Antibodies)
- Dr Heidi Soboll (participant in the NIBSC project of Blood Typing International Standards; PEI Testing Laboratory for IVD)
- Dr Gabriele Unger (coordination of the Collaborating Centre, Training of Assessors programme; PEI unit L3, Public Relations)
- Dr Uwe Unkelbach (head of PEI section 7/3, Batch Release, Blood Products, Albumin, Logistics)
- Dr Gerd Werner (head of PEI section 7/5, Inspections)