



Paul-Ehrlich-Institut
Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines



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

ANNUAL REPORT 2009



Paul-Ehrlich-Institut (PEI)
WHO Collaborating Centre for Quality Assurance of
Blood Products and in vitro Diagnostic Devices

Annual Report 2009

Reporting period August 2008 – June 2009



Head of the centre:
Professor Rainer Seitz
Phone: +49 6103 77 2600

Coordinator:
Dr Gabriele Unger
Phone: +49 6103 77 7010

Fax: +49 6103 77 1250
E-mail: whoccblood@pei.de // whoccidv@pei.de



Paul-Ehrlich-Institut (PEI)
Federal Institute for Vaccines
and Biomedicines
Phone: +49 6103 77 0
Fax: +49 6103 77 1234
URL: www.pei.de

Paul-Ehrlich-Straße 51 – 59, D – 63225 Langen, Germany

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



Contents

Preface	1
Part I –Terms of Reference as designated in June 2005.....	3
General Framework	3
Part II – Implementation of the work plan in relation to the terms of reference..	4
1. PEI contribution to the development of specific WHO projects on quality assurance and safety of blood products and in vitro diagnostic devices (IVD)	6
1.1 Blood Regulators Network (BRN).....	6
1.2 Secondments to WHO headquarters	8
2. PEI contributions to the WHO Expert Committee of Biological Standardization (ECBS) and related meetings and consultations.....	11
2.1 59th ECBS Meeting, Geneva, Switzerland, 13 – 17 October 2008	11
2.2 Meeting with WHO Collaborating Centres to support the development of WHO Biological Reference Preparations (BRP) for high risk blood safety-related in vitro diagnostics (IVDs) and for potency determination of blood products, Paul-Ehrlich-Institut, Langen, Germany, 17 – 19 February 2009	12
2.3 International Nonproprietary Names (INN) of blood products and monoclonal antibodies	17
3. Contribution in the establishment of WHO International Biological Measurement Standards (IS) and Reference Panels.....	18
3.1 Contribution in the design and organization of collaborative studies in order to establish WHO International Biological Measurement Standards (IS) and Reference Panels.....	18
3.2 Participation in WHO Collaborative Studies organized by other WHO Collaborating Centres.....	22
4. Contribution to the development of guidelines and recommendations.....	23
5. 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.....	24
5.1 ICDRA Meeting 2008, Berne, Switzerland, 16 – 19 September 2008	24
6. Training courses offered to assessors working in regulatory authorities.....	26
6.1 Trainee from the HIV Testing Section, Department of Medical Sciences (DMSc), National Institute of Health, Thailand, August 2008	26

6.2	Trainee from the Public Health Laboratories Directorate of Vaccines Control and Blood Products Laboratory, Ministry of Health, Syrian Arab Republic, October 2008.....	26
6.3	Trainee from the Biologics Department of the National Institute for the Control of Pharmaceutical and Biological Products (NICPBP), China, June – July 2009.....	26
6.4	Trainee from the National Organization for Research and Control of Biologicals, Egyptian National Regulatory Authority (ENRA), Egypt, June – July 2009.....	27
6.5	One day visitors of the PEI WHO Collaborating Centre	28
7.	Other WHO Meetings, related to PEI WHO CC activities.....	30
7.1	9th General Annual Meeting of the Global Collaboration for Blood Safety (GCBS), Geneva, Switzerland, 12 – 14 November 2008	30
7.2	Joint workshop of the World Federation of Hemophilia (WFH) and WHO on regulatory issues relating to plasma-derived products, Kuala Lumpur, Malaysia, 22 – 24 October 2008	31
8.	Other (non- WHO) meetings and workshops, related to WHO and PEI CC activities (chronological order)	32
8.1	Global Health Forum (23rd Forum on Global Issues), Ministry of Foreign Affairs, Berlin, Germany, 18 March 2009	32
8.2	16th IPFA/PEI NAT Workshop on Surveillance and Screening of Blood Borne Pathogens, Brussels, Belgium, 26 – 27 May 2009	33
8.3	SoGAT (Standardization of Gene Amplification Techniques) – Blood Screening, Brussels, Belgium, 28 – 29 May 2009.....	33
Professional staff involved in the activities of the WHO Collaborating Centre		34
Publications of PEI colleagues of the WHO Collaborating Centre.....		36

Preface

The Paul-Ehrlich-Institute (PEI) was designated as a WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices in June 2005. The fourth annual report of the PEI presented here describes the activities during the last year of the first designation period.

The PEI, following the vision of its founder, the Nobel Price laureate, Paul Ehrlich, is unique in serving a dual function: to combine excellence in regulatory work with a high level programme of experimental scientific research. Thus, scientific competence, in both the assessment of dossiers submitted by applicants and the control and standardization work in the laboratories, is fostered by experimental research. On the other hand, questions arising from the regulatory work stimulate research projects.

In 1994, the PEI became the German federal senior authority responsible for blood products, as a consequence of virus transmissions by blood products. The safety of medicinal products derived from blood is nowadays ensured through numerous official functions of the PEI. In Germany, blood components for transfusion are subject to the German Medicinal Products Act ("The Drug Law") and require a national marketing authorization granted by the PEI. Plasma derivatives are mostly licensed in cooperation with other European authorities, using mutual recognition, or decentralized procedures. Biotechnology products, such as recombinant coagulation factors, have to undergo a marketing authorization procedure through the European Medicines Agency (EMA), based in London, using a centralized procedure. The PEI is involved in a large proportion of the scientific assessment of products in European procedures, acting as rapporteur, co-rapporteur, or as the reference member state. Acting as experts, PEI scientists participate in most of the scientific committees of the EMA. They chair several working parties, and provide significant input into drafting guidelines and providing of scientific advice. The PEI plays an important role in the Official Medicines Control Laboratory (OMCL) network coordinated by the European Directorate for the Quality of Medicines and HealthCare (EDQM) based in Strasbourg, France, responsible for about half of batches released within the EC. Official batch release includes laboratory testing and review of source material and manufacturing documentation. Further areas of regulatory work include inspections in cooperation with regional authorities, haemovigilance and pharmacovigilance with the ability to enforce corrective measures, contributing to the drafting of important legal and guidance documents, as well as the provision of advice and information to health politicians and the public.

Of crucial importance for the prevention of the transmission of pathogens by blood products are sensitive and reliable test methods to detect markers of infection. Indeed, the PEI has long-standing experience of the regulatory control of in vitro diagnostic devices and performs extensive laboratory research in this field. The continuous independent assessment of test kits by the PEI has been an important driving force in the optimization of assays and in helping industry to improve their products. It is particularly valuable to have the regulatory responsibility and the laboratory capability to perform competent experimental assessments and research within the same institute.

The PEI is committed to continue working with the WHO, in its goal to support the development of effective blood systems all over the world, and to advance globally the quality and safety of blood products. Thus, the PEI decided to apply for redesignation as WHO Collaborating Centre in order to provide continued support to WHO.



Rainer Seitz
July 2009

Part I –Terms of Reference as designated in June 2005

General Framework

The overall objective of the terms of reference for the Paul-Ehrlich-Institut (PEI), as a WHO Collaborating Centre (CC), 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) recognises the importance of this to public health and offers WHO the expertise and cooperation in this area of work.

During the period of time covered by this annual report (August 2008 – June 2009) PEI has supported WHO activities and human resources for the development of specific projects and meetings focusing on the promotion of regulatory networks and appropriate regulations for blood and blood products. Special efforts were also devoted to international standards in the IVD area. The PEI's first success was the completion of the standardization project for anti-HBc. The report, proposing the establishment of the 1st International Standard for anti-HBc was adopted by ECBS in October 2008. This long-awaited standard is expected to be pivotal in the determination of the analytical sensitivity and quality of anti-HBc assays worldwide.

PEI is involved in the organization of training courses and meetings concerning regulatory control systems, and the institute has extensive experience in the regulation and control of blood products and plasma derivatives, as well as in vitro diagnostic devices (IVDs). It is in these areas that PEI has actively contributed to the WHO activities on quality assurance and safety of blood and related biologicals.

Participation in laboratory and standardization programmes and WHO collaborative studies with the aim of establishing international standard preparations and reference panels has also been part of the work plan during 2008 / 2009.

Details of these activities are described in Part II.

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

Dr Margaret Chan, the Director-General of WHO, visited Germany following the invitation of the German Minister of Health, Ulla Schmidt on the 18th March 2009. After her inspiring and empathic address at the Global Health Forum (23rd Forum on Global Issues) at the Ministry of Foreign Affairs in Berlin (see WHO homepage http://www.who.int/dg/speeches/2009/financial_crisis_20090318/en/index.html), Dr Chan used the opportunity to meet representatives of senior federal authorities, including the Bundeszentrale für gesundheitliche Aufklärung, BZgA, the Robert Koch-Institut, RKI and the Paul-Ehrlich-Institut, PEI. Professor Johannes Löwer and Dr Gabriele Unger, who had also attended the Global Health Forum (see point 8.1), outlined the collaboration of the Paul-Ehrlich-Institut with the World Health Organization. Professor Löwer stressed that PEI will further support developing countries in their endeavours to raise the level of quality and safety of blood products.

Dr Chan expressed her appreciation of the institute's commitment and emphasized that the work of WHO is to a major extent dependent on the contribution of the WHO Collaborating Centres. Common objectives and critical points were openly discussed as well.



Professor Burger, Vice President of RKI welcomes Dr Chan, the DG of WHO and Marc Danzon, DG of WHO/EURO¹ to the Robert Koch-Institut, Berlin

¹ Photographs by Hans Günter Bredow, Robert Koch-Institut



Dr Chan (middle), Ms Knufmann-Happe, ADG, German Ministry of Health (left), and Dr Danzon, during the discussions at the Robert Koch-Institut¹



Dr Burger (RKI), Professor Löwer, and Dr Unger (both PEI) (from left to right)¹

Presentations of the WHO Collaborating Centres ¹



¹ Photographs by Hans Günter Bredow, Robert Koch-Institut

1. PEI contribution to the development of specific WHO projects on quality assurance and safety of blood products and in vitro diagnostic devices (IVD)

1.1 Blood Regulators Network (BRN)

Following a recommendation of the 11th International Conference on Drug Regulatory Authorities (ICDRA, Madrid, Spain, 16 – 19 February 2004), the formation of a global network of regulatory authorities for blood and blood products was proposed at the annual meeting of the WHO Expert Committee on Biological Standardization (ECBS) in Geneva, Switzerland in 2005. The terms of reference of the Blood Regulators Network (BRN) were finalized in June 2006, and the first meeting of the BRN took place during the 56th ECBS Meeting, Geneva, Switzerland, 23 – 27 October 2006.

Consistent with the recommendations of the ECBS, the WHO BRN addresses issues related to advancing technical expertise in the areas of blood, blood products and associated drugs and medical devices including in vitro diagnostic devices (IVDs). Particular emphasis lies on reacting quickly and flexibly to critical situations.

The BRN work focuses on:

- 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;
- exploration of opportunities among regulatory authorities to cooperatively address emerging public health challenges;
- exploration of opportunities for regulatory collaboration/harmonization.

The BRN comprises six recognized regulatory authorities (referred to as "Members") which are responsible for the regulation of blood, blood products and related in vitro diagnostic devices (IVDs), and possesses the necessary expertise and capacity to address emerging public health challenges. Members are (in alphabetical order of country): Therapeutic Goods Administration (TGA), Australia; Health Canada, Canada; Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), France; Paul-Ehrlich-Institut (PEI), Germany; Food and Drug Administration (FDA), USA, and Swissmedic, Switzerland. Each authority is represented by a member and an alternative member. The PEI representatives are Professor Rainer

Seitz, who served for two years (2006 to 2008) as the first BRN chairperson, and Dr Margarethe Heiden.

The BRN reports to the ECBS and assembles at least annually during the regular ECBS meeting at WHO headquarters in Geneva. A consultation took place during the ECBS meeting in October 2008. Further face-to-face meetings are organized as appropriate, e.g. by taking advantage of the participation of BRN members in high-level international meetings. Such a meeting was hosted by Health Canada in Ottawa, Canada, 28 – 29 March 2008. Another face-to-face meeting was held during the ICDRA meeting in September 2008 in Bern, Switzerland. In addition, teleconferences are organized as required; in 2009, BRN telephone conferences took place in March, May and June.

WHO/HSS/EMP/QSM/QSD (WHO Cluster Health Systems and Services/ Department of Essential Medicines and Pharmaceutical Policies / Unit Quality Assurance and Safety of Medicines / Quality Assurance and Safety: Blood Products and Related Biologicals Team) provides secretarial support for the activities of the network and acts as a central repository of information and documentation. The WHO provides the BRN members with a restricted web tool, facilitating the exchange of messages and documents. The actual items of discussion, and the minutes of BRN meetings and teleconferences are confidential. However, general information about the BRN is available on the WHO web site, and documents produced by the BRN for publication are posted: <http://www.who.int/bloodproducts/brn/en/>. Documents published so far include BRN position papers addressing the donor selection in pandemic situations, the use of older vs. younger stored RBC (red blood cells), as well as the collection and use of convalescent plasma in an influenza pandemic.

1.2 Secondments to WHO headquarters

1.2.1 *Dr Heinrich Scheiblaue* (unit PEI Testing Laboratory for IVDs), 14 April 2008 – 13 March 2009

Dr Scheiblaue was working with Dr Ana Padilla (supervisor) in the Quality Assurance and Safety: Blood Products and Related Biologicals (QSD) Team within the unit of Quality Assurance and Safety of Medicines (QSM), Department for Essential Medicines and Pharmaceutical Policies (EMP), in the Health Systems and Services (HSS) cluster.

The scope of the secondment included activities relating to the establishment and appropriate use of WHO Biological Reference Preparations (BRPs) and the impact on the regulation and control of blood related diagnostic tests at a global level, as well as in the regulation of blood and blood products safety. His main activities comprised the following:

- Organization of a conference with experts in the field of Chagas diagnostics, in May 2008 in Geneva, in order to agree on the type of reference materials and protocol for the collaborative study.
- Presentation of the WHO strategic plan for the development of WHO Biological Reference Preparations (BRPs) for blood safety-related IVDs, given at the IVD Summer School Cambridge, UK, 16 – 18 July 2008.
- Establishment of the 1st International standard for anti-HBc; adoption at the ECBS meeting in October 2008. The report has been published on the WHO webpage http://whqlibdoc.who.int/hq/2008/WHO_BS_08.2008_eng.pdf: “Report of the WHO collaborative study to establish the First International Standard for detection of antibodies to Hepatitis B core antigen (anti-HBc), human plasma” (see also point 3.1.1).
- Organization of the 2nd WHO consultation on the development of a WHO Reference Panel for the control of Chagas diagnostic tests in Geneva, Switzerland, from 27 until 28 January 2009. The meeting was to initiate the international collaborative study for the establishment of the WHO BRPs for quality control of Chagas diagnostic tests.
- Finalization of the Report for the 1st WHO Consultation on International Biological Reference Preparations for Chagas Diagnostic Tests, WHO headquarters, Geneva, Switzerland, 2 – 3 July 2007

http://www.who.int/bloodproducts/ref_materials/WHO_Report_1st_Chagas_BRP_consultation_7-2007_final.pdf).

- Organization of the 2nd Meeting of the WHO Collaborating Centres for biological standardization to support the development of WHO Biological Reference Preparations for high risk blood safety related in vitro diagnostics and for potency determination of blood products. The meeting was held at PEI from 17 to 19 February 2009.
- Support in the development of technical documents and advocacy for the WHO International Standards for Hepatitis B surface antigen and anti-hepatitis B immunoglobulin.
- Revision and update of the WHO Biological Reference Preparations catalogue, including the standards and reference preparations for the regulation and control of blood safety related in vitro diagnostic tests (WHO web site http://www.who.int/bloodproducts/catalogue/alph_March2009.pdf).
- Attendance and support of other standardization projects that were presented at the ECBS 2008. These include the replacement of the 1st International Standard for hepatitis B immunoglobulin, the replacement of the 1st International Standard for parvovirus B19 DNA, the proposal to prepare a parvovirus B19 genotype panel, discussion on the replacement of the TOXM standard, reference reagents to standardize haemagglutination testing for anti-A and anti-B in normal IVIG (intravenous immunoglobulins), PEI contributions to the WHO Expert Committee of Biological Standardization (ECBS), and related meetings and consultations.

1.2.2 Dr Gerd Werner (section Inspection Services for Biological Medicinal Products), 13 October 2008 – 12 October 2009

Dr Gerd Werner has been working with Dr Ana Padilla (supervisor) in the Quality Assurance and Safety: Blood Products and Related Biologicals (QSD) Team within the unit of Quality Assurance and Safety of Medicines (QSM), Department for Essential Medicines and Pharmaceutical Policies (EMP), in the Health Systems and Services (HSS) cluster.

The scope of the secondment includes activities relating to the establishment of a WHO Guideline on Good Manufacturing Practice (GMP) for Blood Establishments, as well as in the regulation of blood and blood products safety. The main activities comprise the following:

- Preparation of a draft WHO guidance document on GMP for the production of blood components, including plasma for fractionation. The goal for the ECBS meeting in 2009 is to obtain approval for distribution of the draft document for official consultation.
- Attendance at the ECBS meetings in 2008 and 2009 and the Global Collaboration for Blood Safety (GCBS) meeting at WHO headquarters, Geneva, Switzerland in 2008.
- Facilitation at the "Regional workshop on GMP for blood / plasma collection establishments", Teheran, Islamic Republic of Iran, 1 – 4 November 2008.
- Establishing of an international network of collaborative organizations (regulatory agencies, blood establishments and other groups) interested in GMP.
- Organization of regional/global workshops on GMP for blood establishments (including regulatory agencies and fractionators) in support of the guideline development.
- Updating the web site on GMP with the material mentioned above: <http://www.who.int/bloodproducts>.

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

2.1 59th ECBS Meeting, Geneva, Switzerland, 13 – 17 October 2008

PEI activities as a WHO Collaborating Centre are closely linked to ECBS. Professor Johannes Löwer and Dr Michael Chudy participated in the plenary session on the first day. The report on the activities of the WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices was presented by Dr Chudy. Professor Löwer informed the audience on the German initiative for a World Health Assembly (WHA) resolution on the availability, safety, and quality of blood products.

In the mean time a draft, which had been written primarily by Professor Seitz, was submitted by the Member States of the European Union to the WHO Executive Board (EB) at the 125th meeting in May 2009. The initial comments from several EB members were extremely positive. It was decided to include the topic on the agenda for the 126th EB meeting in January 2010 for further discussions and decisions.

The report on the activities of the BRN was prepared by Professor Rainer Seitz and presented by his successor as chair person, Dr Jay Epstein (FDA/CBER, USA).

A lengthy discussion on the first draft of the WHO Guideline for Abbreviated Licensing Pathways for Certain Biological Therapeutic Products, WHO/BS/08.2101 took place. The Paul-Ehrlich-Institut had expressed its concerns in a letter to the ECBS Secretariat prior to the meeting in October. The guideline was revised in 2009 and will be discussed again at the ECBS meeting in October 2009 (see also point 4.).

2.2 Meeting with WHO Collaborating Centres to support the development of WHO Biological Reference Preparations (BRP) for high risk blood safety-related in vitro diagnostics (IVDs) and for potency determination of blood products, Paul-Ehrlich-Institut, Langen, Germany, 17 – 19 February 2009

The Quality Assurance and Safety: Blood Products and Related Biologicals (QSD) Team within the unit of Quality Assurance and Safety of Medicines (QSM), Department for Essential Medicines and Pharmaceutical Policies (EMP), WHO headquarters convened the 2nd meeting of the WHO Collaborating Centres for biological standardization (WHO CCs), i.e. the National Institute of Biological Standards and Control (NIBSC, UK), the Paul-Ehrlich-Institut (PEI), and the Center for Biologics Evaluation and Research, Food and Drug Administration (CBER/FDA, USA). The meeting was hosted by the Paul-Ehrlich-Institut.

Professor Seitz opened the meeting and welcomed the participants. Professor Löwer, President of the PEI, gave an overview of the history of the PEI and described the current responsibilities, duties and research activities of the PEI. Changes in the regulation of medicines and IVDs in the European Community affect the responsibility and duties in the future. He stated that new products, such as gene transfer products, cell therapy products and engineered tissues had become new responsibility areas of PEI. Further participants of PEI were Dr Michael Chudy (IVD session, rapporteur), Dr Sally Baylis (IVD), Dr Steffen Groß (IVD), Dr Julia Kreß (IVD), Dr Thomas Montag-Lessing (IVD), Dr Sigrid Nick (IVD), Dr Micha Nübling (IVD), Dr Gabriele Unger (sessions IVD, blood products), Dr Johannes Dodt (blood products), Dr Dagmar Dörmann (blood products), Dr Anneliese Hilger (blood products), Dr Andreas Hunfeld (blood products), and Dr Herbert König (blood products).

Just as the first meeting, this meeting focussed on biological reference preparations (BRPs) for IVDs with global importance for blood and blood products safety. Besides the high priority preparations for screening tests of the human immunodeficiency virus (HIV), hepatitis B and C virus (HBV, HCV), BRPs for IVDs of other hepatitis viruses (HDV, HEV), human parvovirus B19 (B19V), human T-cell lymphotropic virus types 1 and 2 (HTLV), herpes-, papilloma-, polyoma- viruses (CMV, EBV, JCV, BKV, HHV8), and arthropod-borne group of viruses (West Nile Virus (WNV), dengue virus, Chikungunya virus, Japanese encephalitis virus) were considered.

Some of the currently most important parasite caused diseases (malaria, Chagas, babesiosis, and toxoplasmosis) were reviewed and the needs for the establishment of BRPs discussed.

Dr Thomas Montag-Lessing of PEI presented a project on the development of panel of blood-borne bacteria which could serve as an international reference panel. The transfusion of blood components containing high counts of bacteria and bacterial toxins may lead to immediate septic shock, multiorgan failure and, not infrequently, to the death of the recipient. Currently, no international standards exist for the investigation of blood component related bacterial contamination. During the meeting of the Subgroup Bacteria Working Party / Transfusion-Transmitted Infectious Diseases (WP-TTID) of the International Society of Blood Transfusion (ISBT) in Macao, 2008, it was decided to organize an international collaborative study to evaluate different blood-borne bacterial strains. Bacterial strains have been selected and characterized according to their capability to multiply in platelet concentrates. A novel procedure has been developed to manufacture the selected bacterial strains as deep frozen suspensions, consisting of living microbial cells only. The outcome of the study demonstrated that the bacterial strains investigated are suitable materials for the use as a reference standard panel. The panel is intended for the development, validation and comparison of methods for both bacteria screening and pathogen reduction. It was proposed to establish these materials as the 1st International Transfusion-Relevant Bacterial Strain Panel.

In the discussion of the WHO CCs it was confirmed that there is a need to ensure the bacterial safety of blood components. Available reference materials used for test validation can contribute to the safety of blood components. The participants supported the PEI proposal to be submitted to ECBS in October 2009 for consideration as WHO Reference Panel.

The participants of the strategy meeting finally agreed on a list of BRP proposals for establishment and for a list of new BRP proposals for endorsement, which should be submitted to ECBS 2009. A list of projects requiring further discussions at expert and stakeholder meetings was also drafted.

Further topics on the agenda were:

- New systems/ platforms: Dr Nick of PEI gave an update on new developments of serological test systems (ELISA) for the detection of HBV, HIV, and HCV. In the European Union (EU) all in vitro diagnostic tests must comply with the requirements of the EU directive 98/79/EC in order to become CE marked. Dr Nick described the ability of currently CE marked HBsAg tests to detect escape mutations. In the past, several tests had shown weaknesses in detecting well described escape mutations. Consequently, some kit manufacturers have improved mutant recognition by using a combination of monoclonal antibodies. With respect to clinical sensitivity, significant

differences were observed for HBsAg screening assays. In 2008, two new HBsAg tests with improved sensitivity were CE marked. One assay can detect HBV infection on average 5.3 days earlier than the previous most sensitive assay. In general, HBsAg tests show a high correlation between analytical and clinical sensitivity. The revised EU Common Technical Specifications (CTS) for blood screening assays now define more strict criteria for HBsAg tests with respect to analytical sensitivity (0.130 IU/ml, related to the WHO 2nd International Standard for HBsAg (00/588)) and require consideration of mutants.

Furthermore, Dr Nick gave an update on the sensitivity of HIV and HCV antibody, antigen and combined antigen/antibody test systems. Recently, new HIV combination assays with enhanced sensitivity have been introduced into the market. In addition, a new highly sensitive HCV core antigen assay has been CE marked. This latter marker may be a useful interesting alternative to NAT for the screening of HCV in low income countries.

A short review of the evolution of NAT assays was given by Dr Nübling. Currently, there are two automated multiplex (HCV, HIV, HBV) NAT tests for screening of blood donations on the market. Results from “head-to-head comparison studies” of the two automated NAT systems performed in France and Australia were presented. Overall, both systems appear similar with regard to different quality features, e.g. genotype sensitivity or analytical sensitivity. One assay might be slightly more sensitive for HBV, while the other assay detects lower levels of HCV or HIV-1. A study performed at PEI on the detection of HBV DNA by several commercial NAT assays in anti-HBc reactive specimens was presented. Most NAT assays (both quantitative and qualitative) consistently missed HBV DNA detection by replicate testing in these low level positive specimens of chronic HBV carriers. Therefore screening for anti-HBc may be an option in low prevalence countries until sensitivity of NAT assays assures consistent detection of HBV DNA in these specimens. High sensitivity of HBsAg assays is still an important issue to cover the early phase of HBV infection.

- Emerging/re-emerging agents and blood safety: Dr Nakhasi, FDA/CBER, raised three basic questions in this context and provided CBER's view and conclusions:
 - Is it in the blood supply?
Measurement and identification of the agent. Development of assays for direct or indirect detection of the agent. Estimation of the donor risks and blood component risks. Estimation of the residual risk (incidence and window period).
 - Is it transfusion-transmitted?
Follow-up of case reports and performing look-back investigations. In some cases data from animal studies could be helpful. Information from prospective and retrospective (repository specimens) studies with linked donation-recipient bio specimens or databases.
 - If transmissible by transfusion, does it have a clinical impact i.e., do recipients of infected products have significant clinical manifestations?
Follow-up of case reports and initiating of clinical studies to evaluate the clinical outcomes. Evaluation of the severity (morbidity, mortality, case-fatality rate, e.g. WNV vs. dengue).
He pointed out the 'Five layers of blood safety' and the FDA approach to optimize each safety layer. Further, Dr Nakhasi gave an update on the following emerging and re-emerging pathogens: dengue virus, Chikungunya virus, West Nile virus (WNV), Plasmodium spp., Babesia spp., Leishmania spp., Trypanosoma cruzi (T. cruzi), HIV drug resistant and recombinant variants, HBV mutants, and agents of bioterrorism (class A).
- Standardization of clinical diagnostics: Particularly real-time NAT assays are replacing traditional diagnostic methods in clinical microbiology laboratories. Dr Minor of NIBSC pointed out that many of the assays are developed in-house and therefore the lack of standardized reference materials could lead to a variability of results within and between laboratories. He presented the approach by the Clinical Virology Network in collaboration with NIBSC/HPA (Health Protection Agency, UK) to develop working reagents for clinical NAT assays. The reagents are being prepared by NIBSC and evaluated in two phases. Proposals for the development of WHO International Standards for CMV DNA and EBV DNA for NAT based assays were accepted by the ECBS in 2008. Targets for future standardization projects are BK virus and JC virus.

The following items and future actions were discussed during the session concerning the determination of potency of blood products:

- problems with the vWF Ristocetin cofactor assay;
- vWF concentrate standard: chance for an assigned potency for collagen binding assays;
- calibration of the WHO 4th IS FIX Concentrate: discrepancy with recombinant FIX;
- potency of recombinant FVIII products: discrepant values with clotting or chromogenic assays.

The reports will be provided on the WHO web site:

<http://www.who.int/bloodproducts/en/index.html>

2.3 International Nonproprietary Names (INN) of blood products and monoclonal antibodies

Since May 2006, Dr Karin Weisser of PEI has been working as "Biological Advisor" for the International Nonproprietary Names (INN, i.e. generic names) expert group in line with the INN programme located at WHO headquarters. The programme is responsible for the selection and publication of INN for new pharmaceutical substances upon request by manufacturers. An INN identifies a pharmaceutical substance or active ingredient by a unique name that is globally recognized and is public property. The selection and publication of INNs fall under the responsibility of the WHO unit Quality Assurance and Safety of Medicines (QSM), Department for Essential Medicines and Pharmaceutical Policies (EMP) in the Health Systems and Services (HSS) cluster. The ECBS is informed about decisions and developments at the annual meeting by a WHO representative of the group.

Biologicals in the PEI's responsibility to which INNs are assigned comprise recombinant blood products, monoclonal antibodies and gene therapy medicinal products.

Dr Weisser assessed and commented on 41 INN requests of biological substances from August 2008 to June 2009. She visited two consultations of the INN expert group (47rd and 48th consultation in November 2008 and April 2009, respectively) where all comments were discussed and decisions on the selection of INNs were taken.

In addition, on 6 – 7 October 2008 an INN Working Group Meeting on Nomenclature for Monoclonal Antibodies (mAb) took place at WHO headquarters where a group of INN experts together with the biological advisors and a representative of industry were invited to review and discuss the current policy of naming monoclonal antibodies. Dr Weisser attended the meeting and contributed to the discussions. The contents of the meeting and presentations are confidential and only for participants.

3. Contribution in the establishment of WHO International Biological Measurement Standards (IS) and Reference Panels

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

PEI has thirty years of experience in the regulation and quality control of in vitro diagnostic devices and fifteen years of responsibility for blood products and plasma derivatives. This expertise, as well as the availability of many different blood screening test systems and laboratory methods, form the basis of the commitment of PEI to support WHO in the standardization of WHO Biological Reference Preparations.

3.1.1 Anti-HBc WHO International Standard

Project leader: Dr Heinrich Scheiblaue

A WHO Collaborative Study was undertaken in 2007-2008 to assess the suitability of a candidate international standard (NIBSC 95/522) for the detection of antibodies to hepatitis B core antigen (anti-HBc) in diagnostic assays. The study was done in close cooperation with the fellow collaborating centres, NIBSC (Dr Morag Ferguson) and CBER (Dr Robin Biswas). The final report can be found on the WHO web page: http://whqlibdoc.who.int/hq/2008/WHO_BS_08.2008_eng.pdf.

In October 2008, the ECBS agreed with the recommendation of the report and adopted the candidate NIBSC 95/522 material as the 1st WHO International Standard for Detection of Antibodies to Hepatitis B Core Antigen (anti-HBc).

The assigned unitage is 50 International Units per ampoule. The units are equivalent to the Paul Ehrlich Unit which has been used previously by most manufacturers worldwide. The existing PEI anti-HBc standard can now be expressed in international units.

The main points of the collaborative study for establishment of the WHO anti-HBc international standard are summarized as follows:

Four different materials were evaluated: (A) the candidate anti-HBc international standard preparation (NIBSC 95/522), (B) the current Paul-Ehrlich-Institut anti-HBc standard (PEI 82), (C) a low positive anti-HBc sample (PEI 108166) from a

hepatitis B virus (HBV) infectious carrier without any other detectable HBV markers, and (D) a quality control panel (CBER Panel #11) of 10 members, prepared from individual donors.

The candidate anti-HBc international standard (NIBSC 95/522) was assessed relative to the current PEI 82 standard which is widely used and has an assigned unitage of 100 PEI units per ml. The potency of the candidate material was 50 U/ml. Determination of analytical sensitivity with the candidate standard provided information about assay performance, i.e. the lower the detection limit, the more likely the assays were to be positive for the additionally evaluated samples (PEI 108166 and CBER Panel #11). Intra-assay and inter-laboratory variation for the candidate material (A) were acceptable. Adequate stability has been demonstrated when stored at -20°C. The candidate standard (A) therefore was found suitable for determination of anti-HBc kit sensitivity, to calibrate secondary standards, and for quality control procedures, e.g. in batch release testing.

The sample PEI 108166, which was also evaluated, was found difficult to be detected by some anti-HBc test kits and can be used to provide information about the sensitivity of anti-HBc assays. This sample will be used at PEI as an additional reference material to estimate a minimum level of sensitivity of anti-HBc test kits.

The CBER Panel #11 was found suitable as quality control material for the testing of anti-HBc test kits and supported commutability of the anti-HBc results obtained with the WHO International Standard 95/522.

3.1.2 WHO HBV Genotype Panel

Project leaders: Dr Micha Nübling, Dr Michael Chudy

The proposed HBV genotype panel (PEI code number 5086/08), intended for use with HBV NAT assays consists of 15 samples and covers the most prevalent HBV genotypes collected worldwide: Samples 1-3 (genotype A), Samples 4-6 (genotype B), Samples 7-9 (genotype C), Samples 10-12 (genotype D), Sample 13 (genotype E), Sample 14 (genotype F), and Sample 15 (genotype G).

An international collaborative study has been performed. The aim of the collaborative study was to evaluate the panel of lyophilized plasma samples containing different HBV genotypes for use in NAT based assays. Each laboratory analyzed the panel samples in parallel to the 2nd WHO International Standard (IS) for HBV DNA (NIBSC code 97/750) representing HBV genotype A2. The samples were tested by each laboratory on three separate occasions by quantitative NATs or on four separate occasions by qualitative NATs. The data were collated and analyzed at the PEI.

Seventeen laboratories from 12 countries participated in the study. A total of 19 sets of data were returned; 16 from quantitative and two from qualitative NAT assays. One laboratory performed sequence and genotype analyses. The majority of NAT assays used were commercially available and based on real-time polymerase chain reaction (PCR). The results showed that the genotypes A–G were detected consistently by the majority of assays, although a small number of tests detected genotypes F and G less efficiently or not at all. Only a few genotype B, C, and E samples were under quantified by two methods. The finding that some NAT assays had reduced detection efficiency with some of the non-A2 genotypes proves the necessity of a well characterized genotype panel in addition to the WHO IS. Residual moisture content was determined to be 0.82% in the final container. This indicates that the panel of lyophilized HBV positive plasma samples is very stable under normal conditions of storage, i.e. at -20°C or below and is therefore suitable for long term use. Ongoing real-time stability studies of the panel members are in progress.

No unitage has been assigned to individual panel members. The report was submitted to the ECBS for consideration at the meeting in October 2009. Based on the results of the collaborative study, it is proposed that the panel should be established as the 1st WHO International Reference Panel for HBV Genotypes for NAT Based Assays.

3.1.3 Parvovirus B19 Genotype Panel (started at NIBSC, UK)

Project leader: Dr Sally A. Baylis, former NIBSC co-worker

Since 2004, European regulatory requirements have stipulated that plasma used in the production of anti-D immunoglobulin and pooled human plasma treated for virus inactivation must be screened to ensure that levels of parvovirus B19 (B19V) DNA do not exceed 10 IU/ μ l. The US Food and Drug Administration (FDA)/Center for Biologics Evaluation and Research (CBER) is currently recommending the screening of all plasma pools for B19V DNA and levels should not exceed 10⁴ IU/ml. Variants of B19V have been identified in the last 10 years and these have been broadly divided into three genotypes. These variant viruses have been defined as species of B19V by the International Committee for the Taxonomy of Viruses and both EDQM and CBER/FDA require that assays detect the different genotypes.

A harmonized approach is required for the detection of these different genotypes by control laboratories, and manufacturers and CBER/FDA have been working with NIBSC and PEI in order to prepare a plasma genotype panel for B19V. The filled panel comprises four panel members; three represent the three main genotypes of parvovirus B19 (1, 2 and 3a), and a fourth panel member is a negative plasma sample, all in a liquid/frozen format. Thirty five laboratories (kit manufacturers, quality control laboratories, manufacturers of plasma-derivatives, blood banks and clinical laboratories) have participated in the collaborative study to evaluate the panel members against the 2nd WHO International Standard for parvovirus B19 DNA. The practical part of the study commenced at the end of October 2008, and the final results were returned by the middle of January 2009. A statistical analysis has been performed and a report has been prepared and circulated to participants for comment.

The majority of the laboratories adequately detected all three genotypes, with only a small number of outlying results for genotypes 2 and 3. Stability studies have demonstrated that the panel members are stable under the recommended storage conditions and suitable for long term use. No unitage has been assigned to the panel members; however the B19V positive samples are in the order to 6 log₁₀ IU/ml.

The final version of the report has been submitted to WHO ECBS for consideration at the next meeting in October 2009. It is proposed to establish the panel as the 1st WHO International Reference Panel for Parvovirus B19 Genotypes.

3.2 Participation in WHO Collaborative Studies organized by other WHO Collaborating Centres

3.2.1 Participation in collaborative studies (CS) of WHO International Blood Product and NAT Standards

The PEI laboratories of the sections Batch Release of Blood Products, Logistics and Molecular Virology took part in several 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, UK. 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.

Date: The following studies were performed between June 2008 and June 2009.

CS: Value assignment of the proposed 6th WHO International Standard for Blood Coagulation Factor VIII and von Willebrand Factor in Plasma Human (07/316) and Stability Study

Method: FVIII Potency: Chromogenic Assay, Clotting Assay;
vWF potency Assay: RiCo

CS: Value assignment to the 8th WHO International Standard for Blood Coagulation Factor VIII Concentrate and the Ph. Eur. BRP for Blood Coagulation Factor VIII Concentrate Batch 4 and Stability Study

Method: FVIII Potency: Chromogenic Assay, Clotting Assay

CS: Establishment of a WHO International Standard for C1-inhibitor

Method: C1-INH Potency: Chromogenic Elastase-Assay

CS: Establishment of a WHO International Standard for HIV-2 RNA

Method: Nucleic acid amplification assays (NAT).

4. Contribution to the development of guidelines and recommendations

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

- WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins, WHO/BS/08.2088.
- WHO Guideline for Abbreviated Licensing Pathways for Certain Biological Therapeutic Products, WHO/BS/08.2101 (see also point 2.1).

As mentioned in Section 2.1, this latter guideline, the so-called Biosimilars Guideline draft resulted in much discussion worldwide. Prior to the EBCB meeting in October 2008, PEI expressed its concern in a respective letter to the ECBS Secretariat.

In recognition of the various comments and proposals for correction, the guideline was completely revised early in 2009. Vaccines and plasma-derived products were excluded from the scope of the guideline and clarification of comparability studies (head-to-head) has been given throughout the document. Professor Löwer, as a member of the WHO Expert Advisory Panel was involved in the subsequent discussions. The guideline has been posted on the WHO web site for public consultation:

<http://www.who.int/biologicals/en/>. The document is available for comment until the 9th of October 2009.

5. 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

5.1 ICDRA Meeting 2008, Berne, Switzerland, 16 – 19 September 2008

The 2008 ICDRA meeting was attended by two representatives of the PEI, Dr Margarethe Heiden, and Professor Rainer Seitz, who both gave presentations in the workshops.

ICDRA Workshop C “Safety and pandemic preparedness”

This workshop considered regulatory issues relevant in pandemic situations, particularly with regard to vaccines, and introduction to PaniFlow, a tool for monitoring drug or vaccine related adverse events during a pandemic.

Dr Margarethe Heiden presented concepts, discussed in the WHO Blood Regulators Network (BRN, see also point 1.1), to address regulatory issues with regard to blood supply, which may arise during a pandemic. In the case of an influenza pandemic, it has to be expected that a large part of the donor population will become ill. Furthermore, the personnel of blood establishments may be considerably affected. The question was, whether it would be possible to relax certain regulatory requirements, in order to recruit further donors (e.g. by admitting donors below 17 years or above 65 years of age), reduce the extent of deferrals (e.g. by allowing less stringent haemoglobin levels), or to ease the work load of the personnel. The BRN position is that a certain adjustment of criteria may be acceptable, but safety testing must not be compromised. In the mean time, the BRN has published a position paper on that topic (<http://www.who.int/bloodproducts/brn/DonorSelectionincaseofPandemicSituations.pdf>).

Dr Jay Epstein (FDA/CBER, USA) presented the proposal to consider the use of reconvalescent plasma as an additional therapeutic option. This topic was taken up by the WHO BRN, and a position paper has recently been published (<http://www.who.int/bloodproducts/brn/BRNPosition-ConvPlasma10July09.pdf>).

ICDRA Workshop C “Emerging disease: regulating blood products”

In this workshop, the continuing shortage of blood products on a global scale was addressed. The urgent need for strengthening regulatory control was emphasized in order to achieve sufficient availability of safe blood and blood products. A particular challenge is the risk of transmission of known and emerging pathogens. Thus, the theme of this workshop was in accord with the objectives of the PEI as WHO CC.

Professor Seitz gave a presentation entitled “Plasma quality: how does it matter?” He emphasized the crucial importance of plasma as starting material for a variety of essential medicinal products, and the significance of quality assurance at all stages from the recruitment and selection of healthy donors, through testing of viral markers and other parameters, up to proper preparation, handling and use of plasma for fractionation. This whole chain should be maintained and controlled according to Good Manufacturing Practice (GMP), in order to create a sustainable supply of safe plasma and plasma-derived products. These principles also describe the spirit of a proposal put forward by the European Union by a German initiative for a WHA resolution concerning availability, quality and safety of blood products (see also point 2.1).

During this workshop, another important project of the WHO BRN was presented by Dr Christian Schärer (Swissmedic, Switzerland) also on behalf of Dr Peter Ganz (Health Canada, Canada). The aim of this project is to elaborate assessment criteria for blood regulatory systems.

6. Training courses offered to assessors working in regulatory authorities

6.1 Trainee from the HIV Testing Section, Department of Medical Sciences (DMSc), National Institute of Health, Thailand, August 2008

A colleague from the Thai National Institute of Health spent four days at the PEI-IVD Testing Laboratory (head: Dr Sigrid Nick) in August 2008.

6.2 Trainee from the Public Health Laboratories Directorate of Vaccines Control and Blood Products Laboratory, Ministry of Health, Syrian Arab Republic, October 2008

One colleague from the Syrian Public Health Laboratories Directorate visited PEI in October 2008 to receive training in the Viral Vaccines section as well as the PEI WHO CC area for Batch Release, Blood Products, Logistics (one week; head: Dr Uwe Unkelbach).

Part of the travel costs was reimbursed by the WHO/EMRO fellowship programme.

6.3 Trainee from the Biologics Department of the National Institute for the Control of Pharmaceutical and Biological Products (NICPBP), China, June – July 2009

A colleague from the NICPBP spent three weeks at the PEI to receive training in the sections Bacterial Vaccines, Quality Management System at PEI, European Coordination, as well as the following PEI WHO CC areas:

- Microbial Safety (one week head: Dr Thomas Montag-Lessing);
- Batch Release, Blood Products, Logistics (one week; head: Dr Uwe Unkelbach);
- Viral Safety (two days; head: Dr Johannes Blümel);
- Monoclonal and Polyclonal Antibodies and Immunochemistry (two days; heads: Drs Jan Müller-Berghaus, Siegfried Giess).

6.4 Trainee from the National Organization for Research and Control of Biologicals, Egyptian National Regulatory Authority (ENRA), Egypt, June – July 2009

A colleague from ENRA spent a week at the following PEI WHO CC areas in order to be trained in specific laboratory techniques:

- Batch Release, Blood Products, Logistics (three days; head: Dr Uwe Unkelbach);
- Monoclonal and Polyclonal Antibodies and Immunochemistry (two days; heads: Drs Jan Müller-Berghaus, Siegfried Giess).

6.5 One day visitors of the PEI WHO Collaborating Centre

6.5.1 *Visit of the Minister of Health of the Socialist Republic of Vietnam and Delegates, May 2009*

The Minister of Health, Minister Nguyen Quoc Trieu and the delegates visited the PEI in May 2009 to exchange experiences and to discuss the regulation of blood products in Germany and Europe. The Vice-President of PEI, Professor Klaus Cichutek provided information on the research programme of the institute and other activities. The delegation visited the laboratory of section Batch Release Blood Products, Logistics. Professor Seitz provided information on the German/ European initiative for a World Health Assembly (WHA) resolution (see also point 2.1).



Minister Nguyen Quoc Trieu (left) and the Vice-President of PEI, Klaus Cichutek

6.5.2 General Department of Preventive Medicine and Environmental Health, Vietnamese Ministry of Health, November 2008

A delegation of the General Department of Preventive Medicine and Environmental Health visited the Paul-Ehrlich-Institut in November 2008. Besides the talks about licensing procedures and laboratory testing of vaccines, the delegation also visited the laboratory of the Microbial Safety section. The delegates were particularly interested in the bacterial safety testing and establishment of the new bacteria panels, which shall be proposed to WHO/ ECBS as International Transfusion-Relevant Bacterial Strain Panel in October 2009.

7. Other WHO Meetings, related to PEI WHO CC activities

7.1 9th General Annual Meeting of the Global Collaboration for Blood Safety (GCBS), Geneva, Switzerland, 12 – 14 November 2008

The GCBS forum draws on the experience and expertise of its participants to promote the dialogue on blood safety issues and practical mechanisms to improve blood safety and transfusion practice. National health programmes should develop policies and strategies to ensure patient safety in blood transfusion. Secretarial support is provided to the forum by the WHO Unit Blood Transfusion Safety (WHO Cluster Health Systems and Services/ Department of Essential Health Technologies, WHO/HSS/EHT/BTS).

The annual meeting of GCBS in 2008 was attended by Dr Uwe Unkelbach. Whilst did not give an official presentation, several parties showed great interest in PEI batch release procedures and enquired about the possibility of training programmes at the PEI.

Experiences of blood transfusion settings around the world were shared with the plenary. Interested participants were also given the opportunity to include updates on collaborations, recent international activities, and new proposals.

For the first time, it was decided to focus on a single topic, education and training, in order to allow more in-depth discussions.

Key topics discussed were:

- education and training
- assessment of needs for education and training
- monitoring and evaluation of education and training
- collaboration in education and training.

Technical as well as organizational and administrative issues were addressed extensively on the final day.

Further information is provided on the WHO web site:

<http://www.who.int/bloodsafety/gcbs/en/>.

7.2 Joint workshop of the World Federation of Hemophilia (WFH) and WHO on regulatory issues relating to plasma-derived products, Kuala Lumpur, Malaysia, 22 – 24 October 2008

The WFH/WHO meeting took place in Kuala Lumpur (Malaysia) and was chaired by Mark Skinner (WFH). About 70 participants from Australia and Asian countries (e.g. Bangladesh, Cambodia, China, India, Indonesia, Japan, Malaysia, Mongolia, Philippines, Singapore, South Korea, Sri Lanka, Taiwan, Thailand, and Vietnam) attended the meeting.

Speakers were invited to discuss issues concerning the licensing, control and regulation of plasma-derived medicinal products. Regulatory issues from an EU perspective were presented by Johannes Dodt, PEI. One aim of the meeting was the improvement of the treatment of haemophilia patients with safe products. The pros and cons of contract manufacture of concentrates were discussed, in comparison to the development of self sufficiency, including domestic fractionation and development of simple treatment options, e.g. SD cryo for haemophilia A. The latter could be an affordable alternative to concentrates. Case studies were discussed in order to support decision making with respect to the choice of treatment and suitability/safety of coagulation factor concentrates.

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

8.1 Global Health Forum (23rd Forum on Global Issues), Ministry of Foreign Affairs, Berlin, Germany, 18 March 2009

Professor Löwer and Dr Unger attended the 23rd Forum on Global Issues. The forum was held at the Ministry of Foreign Affairs and dealt for the first time with health issues. This fact was regarded as evidence of the growing importance of health as a political factor. Pandemics, like SARS in 2003 or avian influenza (“bird flu” H5N1) in 2005 but also global epidemics like AIDS and tuberculosis would reveal the necessity of global (political) coordination in the fight against diseases.

The forum was opened by the Minister of State, Mr Silberberg. He highlighted that about 40 German research institutes are involved in more than 200 WHO projects. The aim of the German government is to assist in strengthening the national health systems of low income countries. The German efforts should be intensified significantly in this field.

Dr Chan, DG of WHO addressed the audience. She expressed her utmost apprehension that the current financial crisis will affect global health care efforts. She pointed out that economic growth has not led to automatic improvement of health as expected by economic experts. Concerned about further restrictions to public health budgets as a result of the crisis, she urged a corrective strategy for social and health politics, as social breakdown might be the consequence (full speech see http://www.who.int/dg/speeches/2009/financial_crisis_20090318/en/index.html, see also first paragraph of part II of this report).

The WHO is regarded as having a key role in the coordination of global collaboration and standard setting.

Further speakers focused on well known hazards and new challenges. Climate change and resistance of microorganisms to antibiotics increase the possibility of further dissemination of infectious diseases such as cholera, diarrhoea, malaria, and dengue fever. On the other hand, continuing urbanization, environmental refugees, and malnutrition (fast food consumption in large cities around the world) bring about new problems like obesity, diabetes, and psychological disorders, only recognized so far as diseases of industrialized countries. But also growing poverty in high income countries leads to severe inadequacies in health care systems and presents risks of social destabilization.

The complete agenda and further information are provided at <http://www.auswaertiges-amt.de/diplo/en/Aussenpolitik/ForumGF/23-GF/Uebersicht.html>

8.2 16th IPFA/PEI NAT Workshop on Surveillance and Screening of Blood Borne Pathogens, Brussels, Belgium, 26 – 27 May 2009

PEI co-organizes annual scientific meetings, primarily on the topics of application of nucleic acid amplification tests (NAT) and other measures to increase blood safety. These meetings are organized in close cooperation with the International Plasma Fractionation Association (IPFA). Standardization is included in the topics discussed at the congress. The recent meeting in Brussels was in direct conjunction with SoGAT (blood screening) which directly followed the IPFA/PEI conference. The IPFA/PEI attracted around 200 attendees again who participated in this two-day congress. From PEI, Dr Heiden discussed the regulatory aspects of pathogen inactivation techniques applied for labile blood components. Dr Nübling, chairman of the Scientific Program Committee, together with Dr Hewlett (FDA/CBER, USA) summarized the presentations and discussions of this conference and announced the next IPFA/PEI meeting which will take place in Zagreb, Croatia in 2010.

8.3 SoGAT (Standardization of Gene Amplification Techniques) – Blood Screening, Brussels, Belgium, 28 – 29 May 2009

In direct conjunction with the IPFA/PEI conference was the XXI SoGAT meeting in Brussels. Again this meeting with two days of interesting discussions focused on the field of standardization of NAT assays. The programme included several topics relevant to standardization efforts and to blood safety. From PEI, contributions were given which included a presentation by Dr Baylis on the new B19 genotype panel and a presentation by Dr Nübling on the “Yield obtained by mandatory HCV- and HIV1-NAT in Germany and break-through transmissions”. Another presentation by Dr Baylis discussed HEV and the need for standardization of HEV assays. Dr Kreß summarized the outcome of the viral NAT proficiency testing programme organized by PEI for German blood banks while Dr Montag-Lessing introduced to the audience the efforts to establish a transfusion-relevant bacterial strain panel. Dr Chudy described the recent progress with the development of the HBV DNA genotype panel established for WHO, while Dr Scheiblauer reported the establishment of the WHO anti-HBc International Standard and the study results.

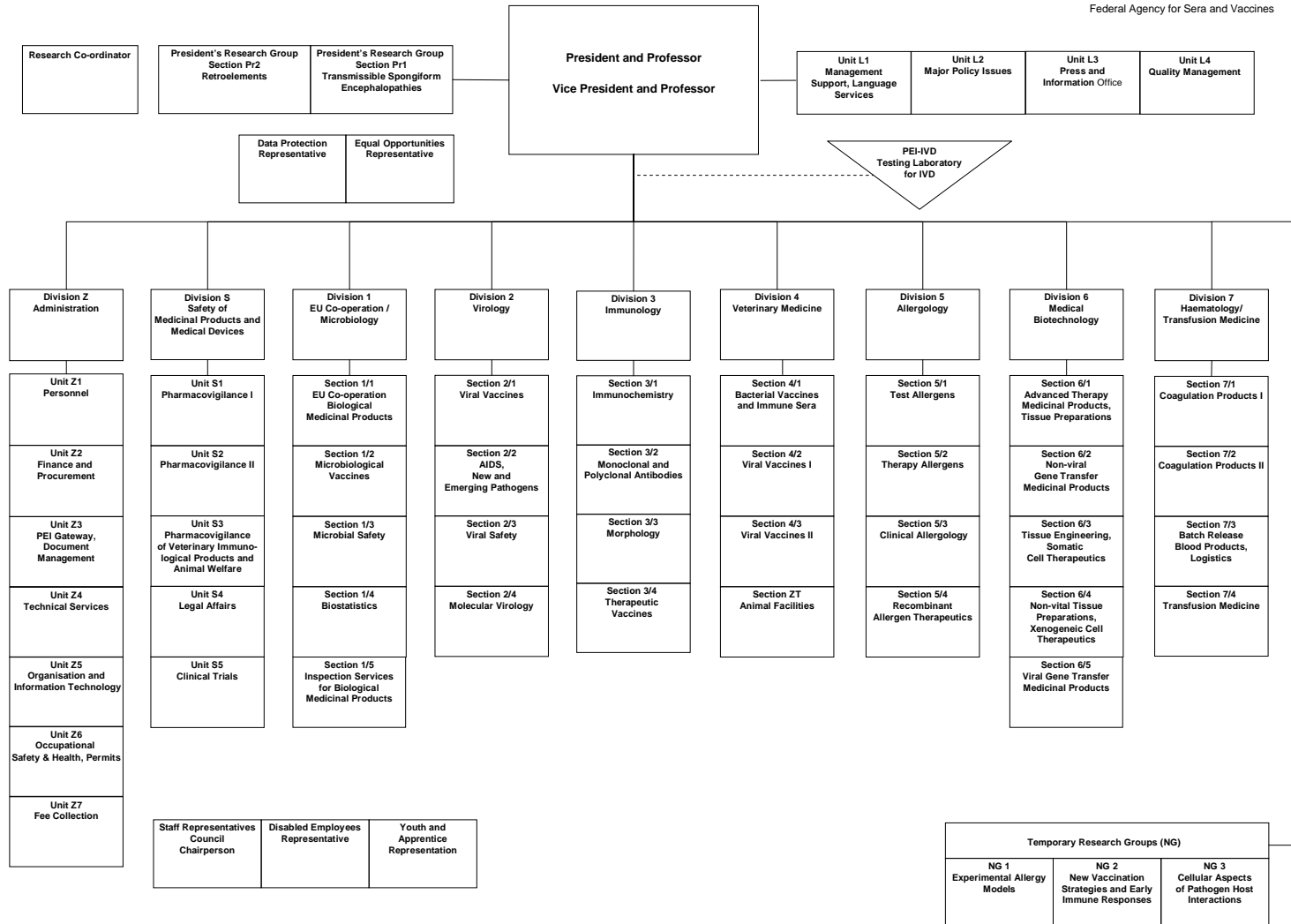
Professional staff involved in the activities of the WHO Collaborating Centre

- Professor Rainer Seitz, head of the WHO Collaborating Centre (head of PEI Division 7, Haematology/ Transfusion Medicine);
- Professor Johannes Löwer, President of the Paul-Ehrlich-Institut;
- Dr Gabriele Unger, coordinator of the WHO Collaborating Centre (Training of Assessors programme; PEI Unit L3, Public Relations, International Relations);

In alphabetical order:

- Dr Sally Baylis (project leader Parvovirus B19 Genotype Panel; PEI Section 2/3, Viral Safety);
- Dr Jan Mueller-Berghaus (head of PEI Section 3/2, Monoclonal and Polyclonal Antibodies);
- Dr Johannes Blümel (head of PEI Section 2/3, Viral Safety);
- Dr Michael Chudy (PEI Section 2/4, Molecular Virology and PEI-IVD Testing Laboratory for IVD);
- Dr Johannes Dodt (head of PEI Section 7/2, Coagulation Products II);
- Dr Markus Funk (head of PEI Unit S/2, Pharmacovigilance II);
- Dr Steffen Groß (Section 3/2, Monoclonal and Polyclonal Antibodies);
- Dr Margarethe Heiden (head of PEI Section 7/4, Transfusion Medicine);
- Ms Sabine Heinz (head of PEI Section 1/5, Inspection Services for Biological Medicinal Products).
- Dr Anneliese Hilger (head of PEI Section 7/1, Coagulation Products I);
- Dr Julia Kreß (PEI Section 2/4, Molecular Virology and PEI-IVD Testing Laboratory for IVD);
- Dr Thomas Montag-Lessing (head of PEI Section 1/3, Microbial Safety);
- Dr Sigrid Nick (head of Unit PEI-IVD Testing Laboratory for IVD);
- Dr Micha Nübling (head of PEI Section 2/4, Molecular Virology);
- Dr Heinrich Scheiblauber (secondment to WHO/HSS/PSM/QSD from April 2008 until March 2009; PEI-IVD Testing Laboratory for IVD);
- Dr Uwe Unkelbach (head of PEI Section 7/3, Batch Release, Blood Products, Logistics);
- Dr Gerd Werner (secondment to WHO/HSS/PSM/QSD from Oct. 2008 until Oct. 2009; former co-worker of PEI Section 1/5, Inspection Services for Biological Medicinal Products).

Paul - Ehrlich - Institut Organizational Chart



As of 1 February 2009

Publications of PEI colleagues of the WHO Collaborating Centre¹

2009

Baylis SA, Nick S, Blümel, Nübling CM. Hepatitis E virus in German blood donors. *Vox Sang* 2009, in press.

Baylis SA, Buchheit KH. A proficiency testing study to evaluate laboratory performance for the detection of different genotypes of parvovirus B19. *Vox Sang* 2009; 97: 13-20.

Eis-Hübinger AM, Weber-Schehl M, Felix Drexler J, Reber U, Panning M, Hedges D, **Baylis SA,** Roth WK, Drosten C. Absence of Detection of Novel Human Parvoviruses in German Plasma Donations. *Transfusion* 2009, in press.

Epstein J, **Seitz R,** Dhingra N, Ganz PR, Gharehbaghian A, Spindel R, Teo D, Reddy R: Role of Regulatory Agencies. *Biologicals* 2009; 37:94-102.

Gravemann U, **Kusch M, König H,** Mohr H, Müller TH. Thrombin Generation Capacity of Methylene Blue-Treated Plasma Prepared by the Theraflex MB Plasma System. *Transfus Med Hemother* 2009; 36:122-127.

Jahn EM, Schneider CK (2009): How to systematically evaluate immunogenicity of therapeutic proteins – regulatory considerations. *N Biotechnol* 25: 280-286.

Nübling CM, Heiden M, Chudy M, Kress J, Seitz R, Keller-Stanislawski B, Funk MB. Experience of mandatory nucleic acid test (NAT) screening across all blood organizations in Germany: NAT yield versus breakthrough transmissions. *Transfusion* 2009, May 18. [Epub ahead of print].

Salge-Bartels U, Huber HM, Kleiner K, Volkerts P, Seitz R, Heiden M. Evaluation of quality parameters for cord blood donations. *Transfus Med Hemother* 2009, in press.

Schmidt M, Korn K, **Nübling CM, Chudy M, Kress J,** Horst H-A, Geusendam G, Hennig H, Sireis W, Rabenau H, Doerr HW, Berger A, Hourfar MK, Gubbe K, Karl A, Fickenscher H, Tischer K, Babiak R, Seifried E, Gürtler L. (2009) First transmission of HIV-1 by a cellular blood product after mandatory nucleic acid screening in Germany. *Transfusion* 2009, in press (available online).

Seitz R, Gürtler L, **Blümel J,** Burger R, Drosten C, Gröner A, **Heiden M,** Hildebrandt M, Jansen B, **Montag-Lessing T,** Offergeld R, Pauli G, Schlenkrich U, Schottstedt V,

¹ PEI co-workers in bold print

Strobel J, **Willkommen H**, Wirsing von König CH (2009): Arboprotozoae. Transfus Med Hemother 36: 8-31.

Seitz R, Beekes M, **Blümel J**, Burger R, von Dewitz C, Gröner A, **Heiden M**, Kretzschmar H, **Nübling M**, Schlenkrich U, Schottstedt V, Strobel J, Willkommen H, Wirsing von König CH, Zerr I (2009): Report of the Working Group 'Overall Blood Supply Strategy with Regard to Variant Creutzfeldt-Jakob Disease (vCJD)'. Transfus Med Hemother 36: 79-93.

Seitz R, Gürtler L, **Blümel J**, Burger R, Drosten C, Gröner A, **Heiden M**, Hildebrandt M, Jansen B, **Montag-Lessing T**, Offergeld R, Pauli G, Schlenkrich U, Schottstedt V, Strobel J, **Willkommen H**, Wirsing von König CH (2009): Arboprotozoen. Bundesgesundheitsbl - Gesundheitsforsch - Gesundheitsschutz 52: 123-146.

Tapp HJ, **Grundmann C**, **Kusch M** and **König H**. Calibrating Thrombin Generation in Different Samples: Less Effort with a Less Efficient Substrate. Thrombosis Journal, 2:6-11, 2009.

2008

Baylis SA (2008): Standardisation of Nucleic Acid Amplification Technique (NAT)-Based Assays for Different Genotypes of Parvovirus B19 -A Meeting Summary. Vox Sang, 94: 74-80.

Baylis SA, Heath A, **Chudy M**, Pisani G, Klotz A, Kerby S, Gerlich W. (2008) WHO collaborative study to establish a replacement International Standard for hepatitis B virus DNA nucleic acid amplification technology (NAT)-based assays. Vox Sang, 94: 358-362.

Fryer JF, **Baylis SA**, Gottlieb AL, Ferguson M, Vincini GA, Bevan VM, Carman WF, Minor PD. Development of working reference materials for clinical virology. (2008). J Clin Virol. 43:367-71.

Gürtler L, **Blümel J**, Burger R, Drosten C, Gröner A, **Heiden M**, Jansen B, Klamm H, Ludwig W-D, **Montag Lessing T**, Gürtler L, Offergeld R, Pauli G, **Seitz R**, Schlenkrich U, Willkommen H, Wirsing von Koenig K-H: Malaria. Transfus Med Hemoth 35:122-134 (2008).

Montag Lessing T, **Blümel J**, Burger R, Drosten C, Gröner A, **Heiden M**, Jansen B, Klamm H, Ludwig W-D, Gürtler L, Offergeld R, Pauli G, **Seitz R**, Schlenkrich U, Willkommen H, Wirsing von Koenig K-H: Arbobacteria-Pathogens Transmittable by Arthropods. Transfus Med Hemoth 35:374-390 (2008).

Neugebauer B, Draï C, **Haase M**, **Hilger A**, **Keller-Stanislawski B**, Laitinen-Parkkonen P, **Mentzer D**, Rasmussen C, Ratignier C, **Seitz R**. Factor VIII products and inhibitor development: concepts for revision of European regulatory guidelines (Letter to the Editor). *Haemophilia* 2008; 14:142-144.

Nübling CM, **Unkelbach U**, **Chudy M**, **Seitz R**. Effect of viral nucleic acid testing on contamination frequency of manufacturing plasma pools. *Transfusion* 2008; 48:822-826.

Padley DJ, Heath AB, Chiodini PL, **Baylis SA** and the Collaborative Study Group. (2008). A World Health Organization International Standard for *Plasmodium falciparum* DNA nucleic acid amplification technology assays. *Malaria Journal*, 7: 139

Pauli G, **Blümel J**, Burger R, Drosten C, Gröner A, **Heiden M**, Jansen HB, Klamm H, Ludwig W-D, **Montag Lessing T**, Offergeld R, **Seitz R**, Schlenkrich U, Willkommen H, Wirsing von Koenig K-H: Influenza Virus. *Transfus Med Hemoth* 35:42-49 (2008).

Pauli G, **Blümel J**, Burger R, Drosten C, Gröner A, **Heiden M**, Hildebrandt M, Jansen B, Klamm H, Ludwig W-D, **Montag Lessing T**, Offergeld R, **Seitz R**, Schlenkrich U, **Willkommen H**, Wirsing von Koenig K-H: Hepatitis E Virus. *Transfus Med Hemoth* 35:50-57 (2008).

Pruß A, Caspari G, Krüger DH, **Blümel J**, **Nübling CM**, Quenzel E-M, Kalusa U, Gerlich G, Gürtler L. (2008). Nukleinsäure-Amplifikationstests für HIV, HBV und HCV bei Gewebespendern: Sinnvoll oder überflüssig? *Transfusion Medicine Hemotherapy* 35, 421–430.

Sharkawi FZ, **Chudy M**, **Hanschmann KM**, **Kress J**, and **Nübling CM**: Consistency of quantitation of HCV genotype 4 from Egypt across three HCV-RNA amplification assays. *J Med Virol* 80(12):2086-91 (2008).

Schneider B, Fryer JF, Reber U, Fischer H-P, Tolba H, **Baylis SA**, Eis-Hübinger, AM. (2008). Persistence of Novel Human Parvovirus PARV4 in Liver Tissue of Adults. *Journal of Med Virol*, 80: 345-351

Schneider B, Fryer JF, Oldenburg J, Brackmann HH, **Baylis SA**, Eis-Hübinger AM. (2008). Frequency of contamination of coagulation factor concentrates with novel human parvovirus PARV4. *Haemophilia* 14:978-86.