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

ANNUAL REPORT 2007

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

Annual Report 2007

Reference period October 2006 – August 2007

Visit of a WHO HTP delegation on 23 August 2007. From right to left: Dr L. Rägo, Dr A. Padilla (both WHO/HTP/PSM/QSD), Dr H. Zucker (ADG of HTP); Professor J. Löwer (President of the Paul-Ehrlich-Institut), Dr G. Unger, Professor R. Seitz (both PEI WHO Collaborating Centre)

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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 and blood derivatives continue to be 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. The medical community learned from the epidemic of virus transmissions such as HIV by blood transfusions and plasma derivatives in the early 1980s. 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) has been the German federal authority responsible for the regulatory control of blood products since 1994. The PEI has manifold official functions 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 of 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 also has longstanding 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 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.

The PEI was designated in June 2005 as WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices. Here, the PEI presents the second annual report.

Rainer Seitz
August 2007

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) considers this request of high relevance in public health and offers WHO the expertise and cooperation in this area of work.

During the period of time covered by this annual report (October 2006 – August 2007) 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 have also been devoted to the international standards in the IVD area.

The contribution to the organization of training courses and meetings in the field of regulatory control systems sharing long-standing and broad experience in the regulation and control of blood products and plasma derivatives as well as in vitro diagnostic devices (IVD) have been part of the active contribution of PEI to the WHO activities on quality assurance and safety of blood and related biologicals.

The active contribution to laboratory studies and standardization exercises and WHO collaborative studies for the purpose of establishing international standard preparations and reference panels has also been part of the work plan during 2006 / 2007.

Details of these activities are described in Part II.

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

On 23 August 2007 Dr Howard Zucker, ADG of WHO HTP, Dr Ana Padilla and Dr Lembit Rägo of WHO HTP/PSM/QSD visited the PEI Collaborating Centre and other parts of the institute. They were able to obtain an impression on the commitment and engagement of all involved persons and the quality and diversity of the work done by the PEI sections which form the collaborating centre. This one day visit provided an excellent opportunity to discuss in depth aspects of mutual interest, and approaches to the common goals reflected by the terms of reference

The official press release and some photographs are attached in Annex I.

1. PEI contribution to 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 now so-called Blood Regulators Network (BRN, as agreed at the ECBS meeting in 2005) were finalized in June 2006. The BRN met for its first working session during the 56th ECBS Meeting, Geneva, Switzerland, 23 – 27 October 2006. Consistent with the recommendations of the ECBS, the WHO BRN will address 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), with a particular emphasis on reacting quickly and flexibly to critical situations. The BRN work the field of blood and blood products will focus on

- scientific assessment of current and emerging threats to the safety and availability;
- 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; and

- exploration of opportunities for regulatory collaboration/harmonization.

For the time being, 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 possess 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. Each authority is represented by a member and an alternate member; representatives of the PEI are Professor Rainer Seitz, who was elected as the first BRN chairperson, and Dr Margarethe Heiden.

The BRN will assemble at least annually during the regular ECBS meeting at WHO headquarters in Geneva. Further face-to-face meetings can be organised as appropriate, e.g. by taking advantage of the participation of BRN members in big international meetings. The BRN will report to ECBS. WHO/HTP/PSM/QSD (Health Technologies and Pharmaceuticals/ Medicines Policies and Standards/ Quality Assurance and Safety: Blood Products and Related Biologicals) will provide secretarial support to the activities of the network and act as a central repository of information and documentation. The WHO provides the BRN members with a restricted web tool, which facilitates the exchange of messages and documents. In addition, teleconferences are arranged, and efficient communication by electronic media is established.

1.2 Secondments

Dr Michael Chudy (unit Molecular Virology and PEI Testing Laboratory for IVD) was seconded to WHO headquarters from 4 September 2006 to 1 August 2007. He was working with Dr Ana Padilla (supervisor) in the unit Quality Assurance and Safety: Blood Products and Related Biologicals (QSD) of the Department of Medicines Policy and Standards (PSM/HTP).

The project of the secondment was the development of an IVD strategic plan to assure the establishment of WHO International Biological Reference Preparations (BRPs) covering microbial agents with relevant 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. This work was part of the strategic plan of PSM/QSD unit for the coming 5 to 7 years.

The establishment of an IVD strategic plan was endorsed by the ECBS at the meeting in October 2006 (presentation Dr Chudy).

A meeting with the three WHO Collaborating Centres (CCs) for Biological Standards and Standardization (NIBSC, CBER, PEI) was organized and held on 29 – 30 January 2007 at CBER/US FDA to strengthen the collaboration among the WHO CCs in order to ensure the continuation of the WHO mandate and leadership in the development of BRPs. The main objectives of the meeting were to coordinate the IVD strategies, to define the priority prospects and to discuss the opportunities for resource mobilization in order to assure the establishment of WHO BRPs. Priority projects were identified to update the existing BRPs for HIV, HBV, HCV, and to continue the establishing of BRPs for the causative agents of syphilis, malaria and Chagas. These BRPs will also be of use with new diagnostic technologies. The WHO CC for Quality Control of Serology in Blood Banks from Sao Paulo, Brazil, was invited to ensure necessary expertise from the Region in discussing the WHO BRP Chagas project. The participation of the AMRO/PAHO Regional Advisors for Blood Services and Biological Products was considered important to strengthen the impact of the WHO Biological Standardization Programme. The recommendations of this meeting will form the five years IVD strategic plan which will be submitted for endorsement to the ECBS in October 2007. A need was emphasized to set up a network of WHO CCs for IVD related biological standardization representing all the Regions in order to ensure complementary and focused expertise at a global level.

The report on the CCs meeting was prepared and posted on the QSD website (http://www.who.int/bloodproducts/en/index.html).

During the period of the secondment, efforts were also made to advance the development of protocols of international collaborative studies and facilitate activities and collaboration of working groups for the establishment of WHO BRPs of the following projects: HBsAg/HBV DNA panel, mono-specific anti-HCV samples, anti-HBc preparation, anti-HBs Ig (replacement), anti-HIV subtype panel, HIV RNA subtype panel, anti-syphilitic preparation (replacement), malaria reference material, Chagas reference material.

As the development of standard materials for Chagas IVD tests was considered as a high priority project at the WHO meeting in January 2007, a WHO consultation was organized and held on 2 – 3 July 2007. Experts in the field of Chagas diagnostics (including WHO collaborating centres for biological standards and standardization, AMRO/PAHO, regulatory authorities, users, and kit manufacturers) discussed at WHO/HQ in Geneva the scientific issues regarding the development of WHO International Reference Preparation(s) for Chagas blood donor screening tests and clinical diagnostic assays. There is consensus that most applicable diagnostic procedures are based on serological methods to detect specific anti-*T. cruzi* antibodies. Appropriate standardization of these tests is urgently needed to ensure the quality of the tests as well as correct serological diagnosis and blood screening. The outcomes of the meeting were: i) a working group of experts on the development of WHO International Reference Preparations was formed; ii) discussion and identification of gaps in standardization of Chagas diagnostic tests, including new technologies; iii) proposals for endorsement and establishment of WHO BRPs for Chagas diagnostic tests by the WHO ECBS (October 2007); and iv) presentation of a plan of action needed for the development of the Chagas reference preparation(s). This meeting was held alongside with the WHO Chagas disease meeting 'From a Latin American Health Perspective to a Global Health Perspective' that took place on 4 – 6 July 2007, WHO/HQ, Geneva, Switzerland, where the outcomes of the WHO consultation were presented.

Presentations on the WHO strategic plan for the development of BRPs for blood safety-related IVDs were given at the SoGAT XX Meeting (Dr Chudy; 12 – 13 June 2007, Warsaw, Poland) and at the annual meeting of the Working Party on Transfusion Transmitted Infectious Diseases (Dr Ana Padilla/ Dr Michael Chudy, 22 – 23 June, Madrid, Spain).

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

2.1 57th ECBS Meeting, Geneva, Switzerland, 23 – 27 October 2006

PEI activities as a WHO collaborating centre are closely linked to ECBS. Professor Johannes Löwer and Professor Rainer Seitz participated in the plenary and presented the report on the activity of the WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices. Professor Löwer and Professor Seitz also took part in the discussions of the blood products and IVD section, and Professor Löwer and Dr Haase (PEI) in the vaccines section. Professor Seitz reported to the plenary about the Blood Regulators Network (BRN) project, which had its first working session during the ECBS meeting. In this session, Professor Seitz was elected as BRN chairman for a term of two years.

2.2 Technical Workshop on Stability of Reference Materials for Biological Medicines and in vitro Diagnostics, Geneva, Switzerland, 27 – 28 November 2006

After the Expert Committee had recommended to start working on the prediction and monitoring of the stability of biologicals in 2004, the appropriate working group was established and endorsed by ECBS in 2005. The group had its second meeting at WHO headquarters in November 2006.

The working group agreed on a written guidance on evaluating the stability of reference materials that should be provided to ECBS as an addendum to the existing WHO recommendations. The guidance should be based on the NIBSC draft guidance notes, which will be worked on further to establish the basis for WHO guidelines. Dr Sigrid Nick of PEI attended the meeting as meeting rapporteur. She presented the main points of presentations and discussions captured during the 2-day meeting.

2.3 Meeting with WHO Collaborating Centres to support the development of WHO Biological Reference Preparations (BRP) for high risk blood safety-related in vitro diagnostics, Washington, USA, 29 – 30 January 2007

The three WHO collaborating centres for biological standardization in the area of blood products and IVD, NIBSC, CBER and PEI met in Washington to develop together with WHO/QSD a strategy plan for the next five years for the establishment of blood safety-relevant IVD reference preparations. Dr Sigrid Nick, Dr Micha Nübling, Dr Heiner Scheiblauer and Dr Gabriele Unger attended the meeting on behalf of PEI (see also secondment report, point 1.2).

The three collaborating centres discussed ongoing and new projects of the following markers which have an impact on blood safety: human immunodeficiency virus (HIV), hepatitis B and C virus (HBV, HCV), and other hepatitis viruses, human parvovirus B19 (B19V), human T-cell lymphotropic virus types 1 and 2, cytomegalovirus (CMV), arthropod-borne group of viruses (West Nile Virus, dengue virus), and human herpes virus 8 (HHV-8). Furthermore, bacterial and parasite caused diseases (syphilis, malaria, Chagas, leishmaniasis, toxoplasmosis) and transmissible spongiform encephalopathies (TSE) caused by the prion agent were reviewed.

The participants of the strategy meeting agreed on a list of priorities that will be presented to the ECBS in 2007. The strategy plan is also intended to be used for fund raising efforts of WHO.

Further topics on the agenda were:

- Epidemiology: possibilities to get relevant epidemiological data of existing and newly arising infectious diseases were discussed. It was agreed that most input should be provided by WHO, i.e. the WHO global blood safety data base, input from WHO Regional Offices and closer links to blood centres. Exchange of information could take place on regularly held WHO CCs meetings and meetings of WHO working groups. Information about urgent incidents could be shared via teleconferences.
- New technologies: Dr Nick reported in Washington on combined antigen – antibody – assays for the detection of HIV and HCV. Dr Nübling talked about the new developments in the NAT area, such as the establishment of Multiplex systems, which cover more and more markers, viral as well as clinical and genetic ones.
  Dr Hewlett described the experience of CBER with microarray assays and nanotechnology.

The participants agreed that (new) WHO BRPs were expected to cover the needs for new technologies as they were similar to biological samples used for any diagnostic assays.

- Future collaboration: all participants agreed that the meeting was very effective and helpful for a closer partnership of the collaborating centres. For most projects two coordinators were named to enhance the cooperation. Annual meetings and possible teleconferences were agreed on as well.

The report is provided on the WHO website:
http://www.who.int/bloodproducts/en/index.html

2.4 INN for blood products and monoclonal antibodies for biologicals

Since May 2006 Dr Karin Weisser of PEI has been working as a ”Biological Advisor“ for the INN expert group in line with the INN Programme located at WHO/HQ. The programme is responsible for the selection and publication of International Nonproprietary Names (INN, i.e. generic names) 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 falls under the responsibility of the HTP/PSM/QSM team of the INN Programme. 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 47 INN requests of biological substances during October 2006 and August 2007. She visited two consultations of the INN expert group (43rd and 44th consultation in November 2006 and May 2007, respectively) where all comments are discussed and decisions on the selection of INNs are taken.

Additionally, on 23 – 24 April 2007 an INN ad-hoc meeting on biologicals took place at WHO headquarters where the INN experts together with representatives of different regulatory institutions and industry were invited to review and discuss the current policy of naming and defining biological medicinal substances. Dr Karin Weisser and Dr Johannes Dodt of PEI attended the meeting and contributed to the discussions by giving a presentation each. The contents of the meeting and presentations are confidential and may be shared by the participants only.

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

PEI has a longstanding expertise in the regulation and quality control of in vitro diagnostic devices and more than ten years of responsibility for blood products and plasma derivatives. This knowledge as well as the availability of many different blood screening test systems and laboratory methods are the basis of the sincere commitment of PEI to support WHO in the standardization of WHO Biological Reference Preparations.

2.5.1 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 might be less sensitive for some HBV genotypes other than A2 which is contained in the current WHO reference preparations. 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 establishing a WHO International Standard Panel of HBV geno- and subtypes was assigned high priority.

Currently Dr Nübling is collecting around 15 different geno-/subtype samples in adequate amounts from different regions of the world. These samples shall be used for both, an HBsAg panel and an HBV DNA panel. A close co-operation with Professor Gerlich (Giessen) has been undertaken. In Giessen, sequencing of HBV in the samples is performed and HBsAg will be purified from the DNA containing Dane particles.

Samples have been acquired from different regions of the world, including South America, South Africa, Europe and Asia. However, adequate concentrations and sufficient volumes of HBV genotypes E and F are not yet covered by the samples obtained so far. During the visit of the WHO HTP delegation on 23 August 2007, Dr Zucker committed himself to making severe efforts at WHO, including responsible persons at headquarter as well as Regional advisors in order to improve the situation of getting biological materials for the establishment of WHO reference preparations.

2.5.2 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. However, the establishment of a WHO International Standard has been regarded as high priority project in several expert meetings, including the ECBS and PEI has been given the lead of the project.

Dr Scheiblauer is currently preparing a WHO collaborative study of various potential anti-HBc standard candidate materials and samples, which were collected or provided to PEI: NIBSC 95/82, CBER anti-HBc panel #11, PEI standard (no. 82), other anti-HBc positive NIBSC material and an anti-HBc low titre clinical sample with an anti-HBc isolated antibody profile ("anti-HBc alone") that could serve as additional reference material ("bench mark control"). These anti-HBc samples were tested at PEI with 14 different CE marked anti-HBc assays. The data were discussed at the meeting of the WHO collaborating centres for biological standards and standardization on 29 – 30 January 2007 (see point 2.3). It was suggested that the NIBSC material 95/522 would be the candidate material for the proposed WHO International Standard for anti-HBc. Other available reference materials, namely of CBER (panel # 11) and of PEI (no. 82), which are currently used for quality control of test kits as well as the anti-HBc low titre sample should be included in the collaborative study.

The WHO Collaborative Study to Establish an International Standard for Anti-HBc has been initiated by contacting various potential participants. A representative number of laboratories worldwide have agreed to participate in the collaborative study. Samples should be ready for shipment in September this year. Laboratory results are expected to be returned by end of the year.

2.5.3 Reference Panel of anti-HCV monospecific samples

Project leader: Dr Sigrid Nick

In 2006, the project was delegated from the former WHO Collaborating Centre Sanquin to PEI. Sanquin project leader Dr Nico Lely had performed a feasibility study in 2004. Meanwhile, a CD with study data arrived at PEI. However, some information like real time stability data is still missing. Besides, the material has not yet been transferred from Chiron who provides the samples. Chiron was asked to test the preparations for infectivity as WHO prefers non infectious standards. It was also asked to introduce additional affinity purification steps to exclude antibodies that react with additional antigens of the recently introduced RIBA version.
Furthermore, WHO contacted Abbott in order to ask for monoclonal monospecific anti-HCV samples. Those samples, if available should be included in the feasibility study as well. The collaborative study is planned for 2008.

2.5.4 Bacteria reference materials

Project leader: Dr Thomas Montag-Lessing

The group of Dr Montag-Lessing has established several bacteria standards in recent years. These bacterial strains are tested for their growth in blood components, especially in platelet concentrates. PEI Bacteria Standards contain only viable cells due to a computer-based production process. They have a defined bacterial count, which is stable for years at -80°C, and they are ready to use. They are intended to be used for the comparison and validation of methods for pathogen reduction of blood products as well as for screening purposes. For experimental imitation of real life conditions leading to the contamination of a blood product, the advantage of these standards is the possibility to contaminate blood components with 0,03 cfu/ml. They were offered as WHO International Reference Preparations forming part of the PEI WHO Collaborating Centre's work plan. During the meeting of the collaborating centres in Washington (see point 2.3) CBER showed a great deal of interest in a collaborative study. Dr Padilla from WHO asked PEI to take the lead for the project and to organize a feasibility study. The data should be presented to WHO and the collaborating centres for biological standardization to make a decision on the priority of the standards. Dr Montag-Lessing is currently preparing the collaboration with interested parties to set up the international study.

2.6 Contribution in WHO collaborative studies organized by other WHO collaborating centres

2.6.1 Participation in collaborative studies of WHO International Blood Product Standards

The PEI laboratory of section Batch Release of Blood Products, Logistics took part in two 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.

International Collaborative Study to establish the 1st International WHO Standard for Alpha-1-Antitrypsin

Date: 02/2006 – 06/2006
Method: Inhibition assay and active site titration of trypsin

SWG Pilot International Collaborative Study to Evaluate Candidates for the WHO 1st IS for Factor XIII Concentrate

Date: 04/2006 – open
Method: Pefakit FXIII incorporation assay (Pentapharm),
FXIII- potency test

2.6.2 Current activities in the standardization of immunoglobulins

Anti-hepatitis B, immunoglobulin replacement standard

The existing WHO standard, the 1st International Reference Preparation (IRP), 1977, as well as the U.S. Hepatitis B Immune Globulin (HBIG) Reference Standard, Lot 2, derive from the same bulk except that the 1st WHO IRP was further diluted and freeze dried. Both standards are crucial for the standardization of anti-HBs potency assay procedures for HBIG or HBIGIV products and for meeting the minimal anti-HBs specification in immune globulin intravenous (IGIV) products. They are used at the Paul-Ehrlich-Institut for batch release testing of several anti-hepatitis B immunoglobulins. It is expected that the number of these therapeutics will increase in the near future due to new applications for marketing authorization.

Further to its utilization as a standard for medicinal products, the 1st WHO International Reference Preparation, 1977, is also used for the quality control of in vitro diagnostic devices for the quantification of anti-HBs antibodies in blood donor as well as patient samples around the world.

The WHO standard (as well as the U.S. standard) will be exhausted in the near future and needs to be replaced urgently, a project that is regarded as being of highest priority by WHO as well as the collaborating centres of biological standardization. Dr Ferguson of NIBSC is the project leader for the establishment of the new material. Dr Steffen Gross of PEI section Monoclonal and Polyclonal Antibodies and Dr Sigrid Nick of the PEI-IVD Testing Laboratory participate in the studies.

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)

3.1 Workshops of the WHO Country Office in Islamic Republic of Iran on Safety of Blood Products and on Biotechnology and Cell Based Products, Tehran, Islamic Republic of Iran, 9 – 13 June 2007

The workshops were organized by the Iranian Ministry of Health & Medical Education, Food and Drug Control Laboratories (FDCL), the Iranian Blood Transfusion Organization (IBTO) and the WHO Country Office in the Islamic Republic of Iran. PEI facilitators were Dr Uwe Unkelbach of the PEI section Batch Release, Blood Products, Logistics and Dr Egbert Flory of the PEI section Tissue Engineering, Somatic Cell Therapeutics.

3.1.1 Workshop on Safety of Blood Products

Dr Mortaza Pirali-Hamedani, Director General of the Food and Drug Control Laboratories (FDCL), as well as Dr Hossein Rastegar, Deputy of Food and Drugs, FDCL, welcomed the audience and introduced the first workshop “Safety of Blood Products”.

Dr Piral-Hamedani stressed the importance of appropriate collecting, storing, cold chain supply and application of blood products to guarantee safety of the products. Consequently, the Iranian Ministry of Health as well as WHO focus on education, operational research and regulatory affaires as important components of the respective strategic plans.

After a presentation by Dr Rastegar about the biological products produced in Iran, Dr Unkelbach introduced the Paul-Ehrlich-Institut and its long tradition in the batch release of biologicals. He highlighted the current tasks and history of the German higher federal authority responsible for the regulation of biologicals such as blood products, vaccines, allergens and veterinary products. In the following hours of the workshop, he reported on the PEI’s experience after more than ten years of batch release of blood products, including the quantity of test methods that had to be established for that purpose as well as the main findings which resulted in the refusal of batch certifications or withdrawal of the marketing authorization of already released batches. He talked about quality problems of solvent-detergent treated human plasma (SD plasma) and finally highlighted the Network of European Department in the Quality of Medicines (EDQM), located in Strasbourg, France, focusing on its

structure and interactions. Detailed lists and duties of this European institution were shown as well.

One evening Dr Unkelbach was offered to visit the private company Bio-Darou, a joint venture with the German BIOTEST company. He was impressed by the high quality of equipment and materials used, as well as the high training standard of the personnel.

3.1.2 Workshop on Biotechnology and Cell Based Products

The second workshop “Biotechnology and Cell Based Products” was also introduced by Dr Pirali-Hamedani and Dr Rastegar. In his speech, Dr Rastegar highlighted the Iranian Testing Laboratory. The specific economic interest of the Iranian government in the field of biotechnology was presented by Dr Mahbodi.

Dr Flory presented the Division of Medical Biotechnology of the Paul-Ehrlich-Institut, which is responsible for the regulation of advanced medicinal products in Germany and also stressed the fields in which basic research is performed.

Specific aspects in the regulation of cell based medicinal products in Europe were considered during the workshop. Dr Flory presented the new European proposal of advanced therapy including tissue engineering products. He explained the official European legally binding definitions and highlighted in detail respective cell based medicinal therapeutics which are also produced in Iran and have been utilized in Iranian clinical trials. The guideline for production and clinical application of cell based products in the European Union (EU) was described by him in more detail. Furthermore he stressed regulatory aspects of gene therapy medicinal products in the EU.

Dr Unkelbach concentrated on the quality management (QM) of batch release and the batch database of the Paul-Ehrlich-Institut. He also presented the new principles of alternative pyrogen testing and its relevance in the verification of established as well as new medicinal products like cell and gene therapeutics. Furthermore, he demonstrated the implementation of this alternative pyrogen test method into European Pharmacopoeia regulations.

The workshop provided the opportunity for intensive discussions between the audience and the respective lecturers. As the location of the workshop was the Pasteur Institute in Tehran, the visit of specific laboratories, e.g. the laboratory for biotechnology, which is performing basic experimental research in different fields including AIDS research, was also possible.

On 14 June, the World Blood Donor Day, Dr Unkelbach was invited to see the Tehran Blood Donation centre & FDCL. He was given the chance to talk to several voluntary blood donors during their donation and thanked them for their commitment. Afterwards he visited the whole donation site including medical examination room, test laboratories, freezing and storage facilities.

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

4.1 Trainees of the Sudanese Ministry of Health at PEI WHO Collaborating Centre, October – November 2006

Two employees of the Sudanese National Drug Quality Control Laboratory, which is a part of the Sudanese Ministry of Health, visited the PEI Collaborating Centre (CC) for training in October / November 2006. The training was proposed by Dr Ana Padilla, WHO headquarters and submitted by WHO/EMRO, Cairo, Egypt (WHO/EMRO fellowship).

Both trainees stayed for six weeks. Besides the units/sections of the PEI Collaborating Centre, other units of PEI were visited as well.

One trainee (A) joined the PEI CC

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

The other trainee (B) joined the PEI CC

- Section 2/5: Viral Safety (head: Dr Johannes Blümel);
- Section 3/2: Monoclonal and Polyclonal Antibodies (head at that time: Dr Christian Schneider);
- Department PEI-IVD: Testing Laboratory for IVD (head: Dr Sigrid Nick);
- Unit S2: Vigilance of in vitro Diagnostics[1] (head: Dr Markus Funk).

Both colleagues were trained at PEI WHO Collaborating Centre sections/ units for 30 days each.

[1] PEI sections were retitled in April 2007

Table 1

Training of Sudanese colleagues 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**	

4.2 Trainee of the Kuwaiti Ministry of Health at PEI WHO Collaborating Centre, June 2007

An employee of the Kuwaiti Ministry of Health spent two weeks at the PEI CC in June 2007. The training was organized by WHO/EMRO, Cairo, Egypt (WHO/EMRO fellowship).

The Kuwaiti colleague stayed at the PEI CC

- Section 1/3: Microbial Safety (head: Dr Thomas Montag-Lessing);
- and visited Section 2/5: Viral Safety (head: Dr Johannes Blümel).

4.3 One day visitors of the PEI WHO Collaborating Centre

A delegation of the Islamic Republic of Iran, namely from the Ministry of Health, the Iranian Blood Transfusion Organization (IBTO), the Iranian Blood Research and Fractionation (IBRF) and Biotest AG, Germany (plasma fractionator) visited PEI Division 7, Haematology and Transfusion Medicine as well as Section 2/4, Molecular Virology in February 2007. PEI unit 7/3 is testing and certifying blood products for Biotest/Iran.

The group was headed by Dr Abolghasemi, Deputy Minister for Health, Ministry of Health and General Director of the (IBTO), Dr Aboofazeli, director of IBRF and Dr Cheraghali, deputy director of IBTO.

Dr Cheraghali strengthened the continuing interest of IBTO to hold a WHO GMP (Good Manufacturing Practice) workshop in Iran with the participation of PEI facilitators in the near future.

5. Other WHO Meetings, related to PEI CC activities

5.1 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, Society for Research and Development), Frankfurt/Main, Germany. WHO is represented by Dr Padilla and Dr Nübling, who is another institutional member as representative of PEI.

At the ISBT meeting 2007 in Madrid, Spain, Dr Nübling introduced two WHO projects for the standardization of biological reference preparations organized by PEI, the HBV geno-/subtype as well as the anti-HBc project (see point 2.5). Both projects received strong support from the audience, and the availability of further HBV genotypes was promised to be checked by different ISBT participants.

5.2 WHO/ISTH (International Society on Thrombosis and Haemostasis) Liaison Group Meeting, Geneva, Switzerland, 7 July 2007

The meeting of the WHO/ISTH Liaison Group took place in Geneva as part of the ISTH SSC (Standardisation and Scientific Committee) Meetings. The meeting was chaired by the ISTH liaison officer, Professor Koen Mertens, and co-chaired by the WHO representative in the Liaison Group, Dr Padilla. Further participants were the chairperson of SSC, a member of the ISTH Council, and WHO CC related to blood: NIBSC, FDA/CBER, and the PEI, which was represented by Professor Seitz.

The Liaison Group endorsed several standard preparations, which had been peer reviewed by recognized SSC experts. These proposals were forwarded to the WHO ECBS for adoption. Also several proposals for new standardization projects were discussed.

5.3 WHO Regional Office for Europe Meeting of Directors of Blood Transfusion Services, Copenhagen, Denmark, 4 – 5 June 2007

The meeting was attended by blood transfusion experts from 49 of the 53 countries in the WHO Region Europe, which covers the whole of Europe and the former Soviet Union to the Pacific coast. For Germany, Professor Seitz took part. The meeting was chaired by Dr Mikhalchuk (Ministry of Health Ukraine). In the first session, representatives from WHO, EU Commission and the Council of Europe EDQM provided their view and priorities regarding blood safety. This was followed by interesting presentations and case studies demonstrating the whole range of diversity of blood systems. There are still countries, where e.g. complete and regular testing of blood donors is not possible due to a lack of resources. However, there are also stimulating projects. The Turkish representative presented the “Club 25”, an organization fostering the recruitment of young donors with manifold activities. The Russian delegate provided information about the construction of new plasma fractionation plants. A paper was elaborated during the meeting in working groups, entitled “Emerging Regionally Shaped Strategic Directions”, which is intended to provide guidance for the development of functioning systems, thus strengthening blood and patient safety.

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

6.1 SoGAT (Standardization of Gene Amplification Techniques), extraordinary meeting at NIBSC, UK, 2 March 2007

Dr Nübling attended the extraordinary meeting on B19 virus. The background of this meeting was the lack of B19 genotypes as reference materials and the problems of commercial NAT systems to consistently pick up the different B19 genotypes (it had been decided by the International Committee on Taxonomy of Viruses (ICTV) that the respective A6- and V9- erythrovirus variants belong to the B19 virus group and represent genotypes 2 and 3). At the meeting different candidate materials were identified to be included in a B19 genotype panel. The panel will be designed and distributed by NIBSC.

6.2 Food and Drug Administration (FDA, USA) Workshop on Immunoglobulins for Primary Immune Deficiency Diseases, Antibody Specificity, Potency, and Testing at the National Institute of Health (NIH), Bethesda, USA, 25 – 26 April 2007

Dr Steffen Gross of PEI participated in the workshop and gave a presentation on "European Perspectives on IVIG[1] Usage and current Testing of IVIGs by the Paul-Ehrlich-Institut".

6.3 XX. SoGAT meeting, Warsaw, Poland, 12 – 13 June 2007

Dr Nübling gave a presentation at this year's SoGAT conference in Warsaw and introduced the HBV projects at PEI (establishment of HBV-geno-/subtype panels, anti-HBc panel) to the SOGAT. Though the main focus of SoGAT is on nucleic acid testing, attention was also paid to both serological projects (HBsAg, anti-HBc).

[1] IVIG: intravenous immunoglobulin

6.4 14th IPFA/PEI NAT Workshop on Surveillance and Screening of Blood Borne Pathogens, Warsaw, Poland, 14 – 15 June 2007

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). Among the different topics of the congress the issues of standardization of both approaches and assays are always represented. The meeting in Warsaw attracted around 180 attendees. Dr Sigrid Nick of PEI gave a presentation on the quality of HBV assays used worldwide and Dr Johannes Blümel of PEI summarized the state of the art concerning screening strategies and pathogen inactivation efforts.

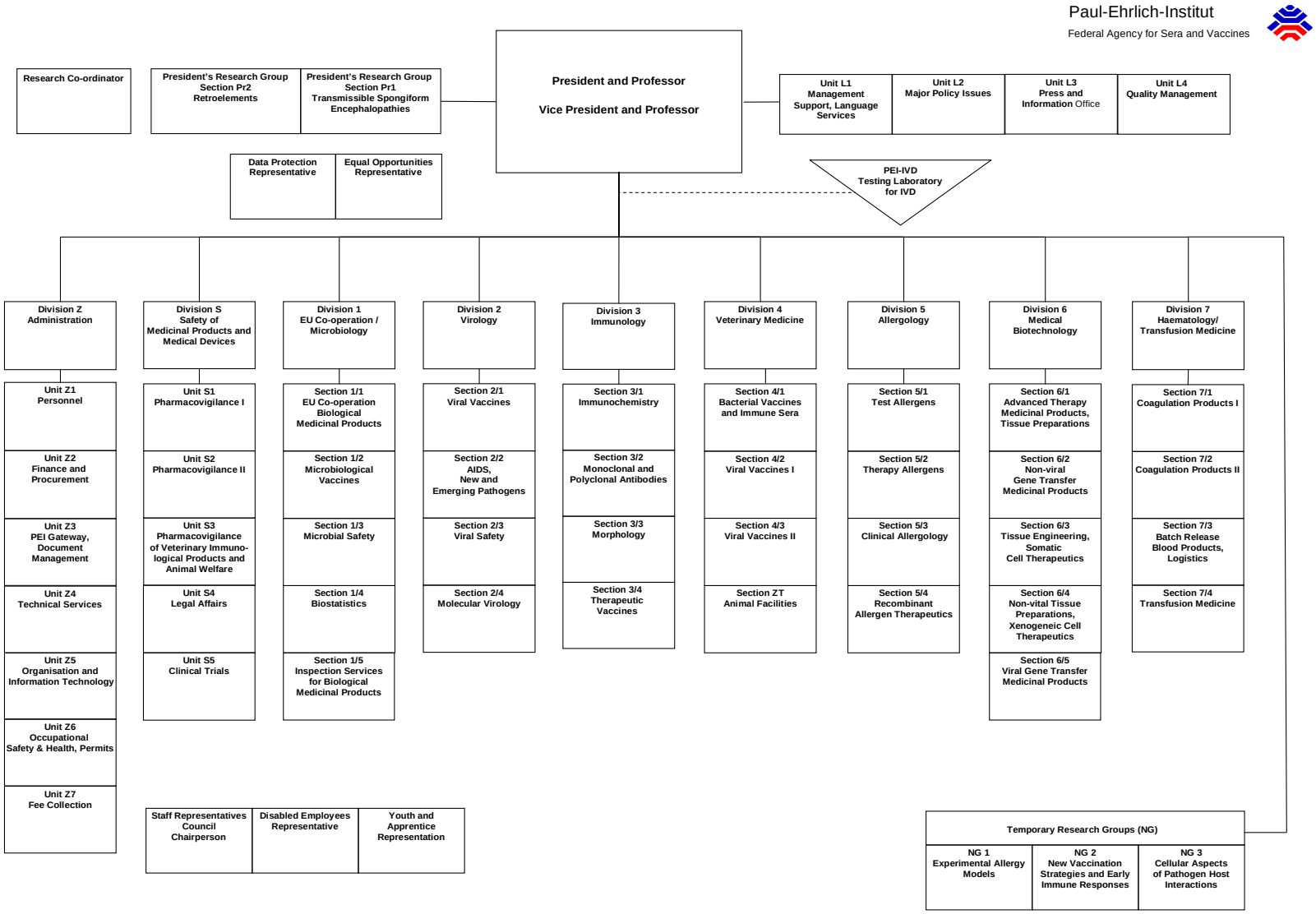
Current list of professional staff of the WHO Collaborating Centre

- 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 2/3, Viral Safety);
- Dr Michael Chudy (secondment to WHO/HQ/PSM/QSD from September 2006 until July 2007; 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);
- Dr Anneliese Hilger (head of PEI Section 7/1, Coagulation Products I);
- Dr Thomas Montag-Lessing (head of PEI Section 1/3, Microbial Safety);
- Dr Sigrid Nick (project leader Anti-HCV Monospecific Samples Reference Panel; head of PEI-IVD Testing Laboratory for IVD);
- Dr Micha Nübling (project leader HBV Geno-/ Subtypes International Standard Panel; head of PEI Section 2/4, Molecular Virology);
- Dr Heiner Scheiblauer (project leader Anti-HBc International Standard; PEI-IVD Testing Laboratory for IVD);
- Dr Jan Mueller-Berghaus (head of PEI Section 3/2, Monoclonal and Polyclonal Antibodies);
- 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, Logistics);
- Dr Gerd Werner (head of PEI Section 1/5, Inspection Services for Biological Medicinal Products).

Paul - Ehrlich - Institut Organizational Chart



As of 1 April 2007

Press Release

Paul-Ehrlich-Institut
Federal Agency for Vaccines and Sera

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WHO Assistant Director-General Howard Zucker's Visit to the Paul-Ehrlich-Institut

On **23 August 2007**, Dr Howard Zucker, Head of the WHO cluster Health Technology and Pharmaceuticals and Representative of the Director-General on Intellectual Property, Innovation and Public Health of the World Health Organization (WHO), was visiting the Paul-Ehrlich-Institut (PEI) at Langen near Frankfurt am Main, Germany. Together with two colleagues (Dr Lembit Rägo, Dr Ana Padilla), he took the opportunity to inform himself on site on the activities of the PEI as WHO collaborating centre for blood products and in vitro diagnostic medical devices. His programme also included the institute's involvement in novel therapies and innovative medicinal products, and he also learned about the publicly accessible database on suspected cases of adverse reactions following vaccination, which has been provided by the PEI on the internet since May 2007.

Dr Howard Zucker was impressed by the regulatory and scientific standard of the institute. As he stated, he was pleased to see that the WHO obviously had made a good choice. According to him, both the collaborative centre and the institute as a whole were showing a high degree of commitment and competence, and a lot could be achieved that way in the years to come.

In June 2005, the PEI had received the WHO's designation as collaborating centre. In this role, the PEI supports the WHO in improving the safety and quality of blood products and in vitro diagnostic medical devices (e.g. HIV tests). In doing so, the Paul-Ehrlich-Institut col-

laborates with the WHO cluster “Health Technology and Phamaceuticals”. With the collaborating centre at the PEI, the WHO has found a strong partner. “We are pleased to make an important contribution to health for everybody by using the entire competence and experience of the institute”, emphasized Professor Rainer Seitz, head of the collaborating centre.

The joint objective is to reach a similarly high standard for blood and blood products worldwide, as already achieved in Germany and Europe.

At the end of the visit, Professor Johannes Löwer, president of the Paul-Ehrlich-Institute stated: “The Paul-Ehrlich-Institut has been committed to safety and availability of biological medicinal products for years, not only in Germany but throughout Europe. We are very happy to see that we can also make a contribution in this field worldwide. “

Dr Howard Zucker has been Head of the WHO cluster Health Technology and Pharmaceuticals and Representative of the Director-General on Intellectual Property, Innovation and Public Health since 2006. He received his B.S. degree in medicine from the McGill University and his M.D. from the George Washington University School of Medicine. After several positions in the field of health at various universities and government institutions, he served as a White House Fellow. Before changing over to the WHO, he was Deputy Assistant Secretary of Health at the U.S. Department of Health and Human Services. Dr Zucker is a member of the U.S. Council on Foreign Relations.

Visit of WHO HTP delegation at the PEI WHO Collaborating Centre on 23 August 2007

Howard Zucker, WHO (right) and Johannes Löwer, PEI with the bust of Paul Ehrlich

Ana Padilla, WHO (right) discussing matters with Sigrid Nick and Heiner Scheiblauer of PEI

Sigrid Nick (right) demonstrates the practical work of the PEI-IVD (in vitro diagnostic devices) Testing Laboratory

Lembit Rägo, WHO (left) explaining WHO view on standardization of reference preparations for IVD. Right: Gabriele Unger and Micha Nübling of PEI