



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 2008



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

Annual Report 2008

Reporting period September 2007 – July 2008



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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

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 third annual report of the PEI is presented here.

The PEI became the German federal higher authority responsible for blood products in 1994. The safety of medicinal products derived from blood is 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. Biotechnological products, such as recombinant coagulation factors, have to undergo marketing authorization through the European Medicines Agency (EMA), based in London, using a centralized procedure. The PEI shares in a large proportion of the scientific assessment of products in European procedures, acting as rapporteur, corapporteur, or as the reference member state. Acting as experts, PEI scientists participate in most of the scientific committees of the EMA, and chair several working parties, and provide significant input into the drafting guidelines and the provision of scientific advice. The PEI performs about half of the EC official batch release, including laboratory testing and review of source material documentation and manufacture, and 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. Further areas of regulatory work include inspections in cooperation with regional authorities, haemovigilance and pharmacovigilance with the ability to enforce corrective measures, contribution to the drafting of important legal and guidance documents, as well the provision of advice and information to health politicians and the public. A guiding principle of the PEI is to combine the regulatory work with a high level programme of 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 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 the test kits by the PEI has been an important driving force in the optimization of tests and helping the 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 work with the WHO, in its goal to support the development of functioning blood systems all over the world, and to advance globally the quality and safety of blood products.

A handwritten signature in blue ink, appearing to read 'Rainer Seitz', with a stylized, cursive script.

Rainer Seitz
September 2008

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 (September 2007 – July 2008) 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 first PEI success has been the completion of the standardization project for anti-HBc. The report, proposing the establishment of the 1st International Standard for anti-HBc will be considered for adoption 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 organization has broad 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.

The active participation in laboratory and standardization programmes and WHO collaborative studies for the purpose of establishing international standard preparations and reference panels has also been part of the work plan during 2007 / 2008.

Details of these activities are described in Part II.

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

Dr Hans Hogerzeil, Director of WHO/ HTP (now HSS, Health Systems and Services) / PSM (Medicines Policy and Standards), visited the Collaborating Centre together with Dr Ana Padilla, Scientist of QSD (Quality Assurance and Safety: Blood Products and Related Biologicals) on 3 March 2008.

They became familiar with the activities of PEI as a WHO Collaborating Centre and the importance of the institute as a leading regulatory authority in the WHO Blood Regulators Network. Dr Hogerzeil gave a presentation concerning “Access to Medicines as Part of Human Rights”, an important issue for the WHO.

Dr Dagmar Reitenbach of the German Ministry of Health (BMG), Multilateral Collaboration attended the meeting as well. She had visited the PEI in December 2007 together with Dr Udo Scholten, Deputy Director General of the BMG Department European and International Health Policy to obtain a personal impression on the international commitments of PEI and especially the collaboration with WHO in various fields.

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 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). A 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; and
- 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 possess 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 representatives of the PEI are Professor Rainer Seitz, who was elected for a term of two years as the first BRN chairperson, and Dr Margarethe Heiden.

The BRN reports to ECBS. The BRN assembles at least annually during the regular ECBS meeting at WHO headquarters in Geneva, which took place also during the ECBS meeting in October 2007. Further face-to-face meetings can be 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 is envisaged during the upcoming ICDRA meeting in September 2008 in Bern, Switzerland. In addition, teleconferences are organized as required.

WHO/HSS/PSM/QSD (Health Systems and Services/ Medicines Policies and Standards/ Quality Assurance and Safety: Blood Products and Related Biologicals) 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, which facilitates the exchange of messages and documents. The actual items of discussion, and the minutes of BRN meetings and teleconferences are confidential. However, on the WHO website, some information about the BRN is available, and documents produced by the BRN for publication will be posted there.

1.2 Secondments

Dr Heinrich Scheiblauber (unit PEI Testing Laboratory for IVDs) has been seconded to WHO headquarters from 14 April 2008 until 13 March 2009. He is working with Dr Ana Padilla (supervisor) in the Quality Assurance and Safety: Blood Products and Related Biologicals (QSD) unit of the Department of Medicines Policy and Standards (PSM), in the Health Systems and Services (HSS) cluster.

The scope of the secondment involves 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. The key terms of reference are as follows:

- organization of an international collaborative study for the calibration of WHO biological reference materials for quality control of Chagas diagnostic tests;
- update of the Work Plan for the WHO Collaborating Centres Network;
- the development of technical documents and advocacy materials to support the appropriate use of WHO International Standards for Hepatitis B surface antigen and anti-hepatitis B Immunoglobulin;
- update of website pages on WHO Biological Reference Preparations for the regulation and control of blood safety related in vitro diagnostic tests.

During the secondment, the anti-HBc standardization project (Establishment of the 1st International Standard for anti-HBc) that was organized by PEI has also been completed and will be considered during the ECBS meeting in October 2008.

The report about the WHO Consultation on International Biological Reference Preparations for Chagas Diagnostic Tests (WHO, Geneva, 2 – 3 July 2007) has been reviewed and updated for publication. In addition, the development of a programme for Chagas reference material has been continued.

A conference was held at WHO headquarters in May 2008 with experts in the field of Chagas diagnostics, in order to agree on the type of reference materials and protocol for the collaborative study. Appropriate standardization of Chagas tests is urgently needed to ensure the quality of the tests, as well as correct serological diagnosis and blood screening. The draft protocol for the Chagas reference preparation will be discussed at the ECBS meeting in October 2008.

Other standardization projects have been presented at the NIBSC Standards Review meeting in March 2008. These include the replacement for 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, reference reagents to standardize haemagglutination testing for anti-A and anti-B in normal IVIG (intravenous immunoglobulins). These will be discussed further at the ECBS meeting in October 2008.

A presentation on the WHO strategic plan for the development of WHO Biological Reference Preparations (BRPs) for blood safety-related IVDs was given at the IVD Summer School (Dr Scheiblaue; 16 – 18 July 2008, Cambridge, UK).

One of the next steps will be to organize a meeting of the WHO Collaborating Centres (CC) for BRP (NIBSC, CBER, PEI) planned for 2009. Topics will be the continuation of the development of BRPs, coordination between the CCs, and discussion of the priority of projects.

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

2.1 58th ECBS Meeting, Geneva, Switzerland, 8 - 12 October 2007

PEI activities as a WHO collaborating centre are closely linked to ECBS. Professor Johannes Löwer participated in the plenary session 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 participated in the discussions of the blood products and IVD section, and Professor Löwer and Dr Öppling (PEI) in the vaccines session. Professor Seitz chaired the BRN meeting on 10 and 11 October.

2.2 Contribution in 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 more than ten 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 sincere commitment of PEI to support WHO in the standardization of WHO Biological Reference Preparations.

2.2.1 Anti-HBc WHO International Standard

Project leader: Dr Heinrich Scheiblaue

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 is being increasingly being used around the world. In order to calibrate test systems, laboratories have requested a primary standard. To date, 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 for many assays. However, the establishment of a WHO International Standard has been regarded as a high priority project in several expert meetings, including the ECBS and PEI has been given the lead on this project.

The report for the establishment of the WHO anti-HBc standard has been finished and provided to the WHO ECBS Secretariat for consideration at the ECBS meeting in October 2008 (WHO/BS/08.2098).

The outcome of the collaborative study is summarized in the abstract of the report:

"A WHO Collaborative Study was undertaken to assess the suitability of a candidate International Standard (NIBSC 95/522) for detection of antibodies to Hepatitis B core antigen (anti-HBc) in diagnostic assays. 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.

Thirteen laboratories from 10 countries tested the materials using 20 different anti-HBc assays. The dilution range of candidate material A was within the dynamic measuring range of assays and the endpoint titres equivalent to the assay's cut-off ranged from 1:33 up to 1:622. As the PEI standard (Sample B) and unit has been used worldwide for many years, the antibody content of Sample A was expressed relative to this standard and unit (100 PEI units/ml). The overall potency of the candidate International Standard A was 50 IU/ml relative to Sample B. Sample C was detected positive by most assays but not consistently in all kits. This clinical sample may provide information about the sensitivity of anti-HBc assays. Similarly, some assays did not detect Panel D members that were specified to be positive. Kits which did either not detect or were weak positive in Sample C were the same that were weak in Panel D, and were also the kits which gave the lowest endpoint titers in the candidate material A and Sample B. Assessing the results quantitatively, low detection limits correlated significantly with positive results and high ratios for anti-HBc concentration measured in Samples C and D. One assay of the study, nevertheless, did not follow this correlation.

For Sample A, within-assay and inter-laboratory variability expressed by geometric coefficients of variation generally were $\leq 16\%$ and $\leq 33\%$ respectively. Stability studies with Sample A stored at 4 °C for over 4 years showed no loss of anti-HBc IgG activity and this indicates long-term stability when it is stored at -20 °C.

The candidate International Standard (NIBSC 95/522) is proposed to be established as the 1st International Standard for the detection of human antibodies to HBcore antigen. This International Standard can be used for calibration of anti-HBc kit sensitivity, to calibrate secondary standards, and for quality control procedures. The potency is proposed to be 50 International Units per ampoule.

Sample C (PEI 108166) was found to be a suitable anti-HBc low reactive sample to show commutability of the proposed International Standard in the different assays and to provide an estimation of a minimum sensitivity of anti-HBc test kits.

Panel D (CBER panel #11) was found suitable as quality control reference panel and also supported commutability of the anti-HBc results."

2.2.2 WHO HBV Genotype Panels

Project leaders: Dr Micha Nübling, Dr Michael Chudy

During the WHO Consultation on Global Measurement Standards and their use in the in vitro Biological Diagnostic Field in June 2004 concern was raised by different participants that 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 especially in developing countries. It was agreed that the subject should be investigated further. During the ECBS meeting in October 2005 the PEI proposed a project to establish WHO International Reference Panels representing different HBV geno- and subtypes. This project was assigned as high priority by ECBS.

Since then Dr Nübling and Dr Chudy have succeeded in collecting several geno-/subtype samples in sufficient amounts from different regions of the world. These highly characterized samples are now being used for the design of both an HBsAg panel and an HBV DNA panel in close co-operation with Professor Gerlich (University of Giessen). In Giessen, HBV genomis sequencing of the samples has been performed and HBsAg content has been determined by an ELISA-independent quantitation approach (i.e. Laurell electrophoresis).

The panel of samples originate from different regions of the world, including South America, South Africa, Europe, the Middle East and Asia. The characterization and design of the proposed HBV-genotypes DNA panel (15 members) is now well advanced. The individual members will be lyophilized during summer/autumn 2008. The project was delayed unexpectedly, due to the closure of the company previously subcontracted by PEI for lyophilization of infectious materials. In the meantime another certified company offering this lyophilization service, under strictly controlled conditions has been identified and audited by Dr Sally Baylis (PEI) and Dr Chudy. After lyophilization of the HBV DNA-containing plasma samples, a collaborative study will be initiated to characterize further the individual panel members by different NAT assays.

The design of the HBsAg panel has been completed. It will contain 15 members, many of them prepared from the same source material as the HBV DNA panel members. This will allow a very detailed characterization of both panels. After final characterization of the putative panel members by Professor Gerlich's laboratory, a pilot study will be performed to investigate the effects of lyophilization on the consistency of detection of HBsAg using different HBsAg ELISA test systems.

After this pilot study, a decision will be made as to whether the HBsAg panel will be lyophilized or prepared in a liquid frozen form for the participants of collaborative study.

2.2.3 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/µl. These regulations have been the result of frequently documented cases of transmission of B19V to recipients of plasma-derived medicinal products, particularly factor VIII concentrates and fibrin sealants where viral loads in products are particularly high given frequent high titres of B19V in plasma start pools. Variants of B19V have recently been identified and these have been broadly divided into three genotypes, and defined as species of B19V by the International Committee for the Taxonomy of Viruses.

A harmonized approach is required for the detection of these different genotypes by control laboratories and manufacturers. This was highlighted at a meeting at the European Directorate for the Quality of Medicines and HealthCare (EDQM) in November 2006 where manufacturers of plasma-derivatives, control laboratories and the producers of parvovirus B19 DNA detection kits met to discuss discrepancies in the performance of certain commercial and in-house assays and the issue of batch release failure. This was elaborated further in March 2007 at the National Institute for Biological Standards and Control (NIBSC, UK), where an extraordinary meeting of SoGAT (Standardization of Gene Amplification Techniques) was held in an attempt to reach a consensus on the preparation of suitable reference materials. It was agreed that a plasma panel, containing high titre B19V samples representing the different virus genotypes, calibrated against the WHO International Standard (IS) for B19V DNA would be the most appropriate formulation. As an interim measure, until the collection of high titre samples of B19V, cloned plasmid DNAs of B19V, were distributed as part of the EDQM Proficiency Testing Scheme (PTS092), co-ordinated by Dr Karl-Heinz Buchheit and scientific advice and materials provided by Dr Baylis. This study highlighted, that whilst progress has been made in the detection and quantitation of different genotypes of B19V, there are still on-going issues and significant under estimation of viral loads of B19V, or complete failure in detection by some laboratories for certain genotypes.

The US Food and Drug Administration (FDA)/Center for Biologics Evaluation and Research (CBER) in the USA, is currently proposing a limit of $\leq 10^4$ IU/ml of B19V DNA for all plasma-derived products. In the future, the FDA may consider B19V testing as donor screening, because of known risks in individuals with chronic anaemia, those who are pregnant or immuno-compromised. Such screening would be dependent upon the availability of suitable commercial kits and sufficient resolu-

tion time. As a consequence of the interest in the USA, the FDA has been working with NIBSC and PEI, in order to prepare a plasma genotype panel for B19V. To this end, high titre samples have been procured and Dr Mei-ying W. Yu (FDA) has organized filling of the panel. Preliminary testing of the samples has taken place at the FDA, PEI and at two testing laboratories in the USA using consensus assays. The filled panel comprises four panel members; three represent the three main genotypes of B19V, and a fourth panel member is a negative plasma sample, all in a liquid/frozen format. Thirty three laboratories (kit manufacturers, quality control laboratories, manufacturers of plasma-derivatives, blood banks and clinical laboratories) have agreed to participate in the collaborative study to calibrate the panel members against the WHO IS. The practical part of the study will commence in October 2008 with results expected to be returned by the end of the year. A proposal has been submitted to the WHO ECBS for consideration at the 2008 meeting to establish the panel as the 1st International Reference Panel for parvovirus B19 genotypes.

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

2.3.1 Participation in collaborative studies of WHO International Blood Product Standards

The PEI laboratory of section Batch Release of Blood Products, Logistics took part in several collaborative studies organized by NIBSC, UK.

Collaborative Study	Type of assay	Result PEI
International Collaborative Study: use of the 1st International (WHO) Standard for Alpha-1-Antitrypsin for recombinant AAT-products	Chromogenic inhibition assay of elastase (E.P. method)	In good correlation with results of other laboratories
International Collaborative Study to establish the 3rd International (WHO) Standard for Antithrombin	Antithrombin chromogenic test	In good correlation with results of other laboratories
Standardization Working Group SWG Pilot International Collaborative Study to Evaluate Candidates for the WHO 1st IS for Factor XIII Concentrate	Pefakit FXIII incorporation assay (Pentapharm) versus FXIII-Activity Method (7/3-A-003)	Not yet started
International Collaborative Study for replacement of WHO International Standard of Blood Coagulation Factor IX	One stage clotting assay	Results outstanding
Collaborative Study for the proposed WHO 2nd International Standard of Factor VIIa Concentrate	Chromogenic and Clotting	Not yet finished
International Collaborative Study for replacement of the current WHO 7th International Standard of Factor VIII concentrate (99/678) and the current Batch 3 Factor VIII Concentrate	One-Stage Clotting and Chromogenic and Fluorogenic	Start mid June 2008
Calibration of the proposed WHO 6th International Standard Factor VIII/VWF Plasma	Chromogenic and One-Stage Clotting and Agglutination	Start September 2008

2.3.2 Current activities in the standardization of immunoglobulins

Anti-hepatitis B, immunoglobulin replacement standard

The current WHO standard, the 1st International Reference Preparation (IRP), 1977, as well as the US 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 utilized for the standardization of anti-HBs potency assay procedures for HBIG or HBIGIV products and for meeting the minimal anti-HBs specification in immunoglobulin 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 based on 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 both blood donor and patient samples around the world.

The WHO standard (as well as the US 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 for 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 participated in the studies.

The PEI results were sent to NIBSC in October 2007 and the final report was prepared by Dr Ferguson. As an outcome of the studies, material no. 07/164 will be proposed to ECBS as 2nd International Standard for hepatitis B immunoglobulin with an assigned potency of 100 IU/ampoule. This material is suitable for verifying therapeutic immunoglobulins, the sensitivity of assay kits and the immune status of vaccines and naturally infected individuals. The wording for preparation of the standard solution was revised to ensure a consistent procedure.

2.3.3 Participation in a collaborative study to evaluate a replacement for the 1st International Standard for Parvovirus B19 DNA

Drs Michael Chudy and Johannes Blümel participated in a collaborative study organized by NIBSC, to evaluate a replacement for the 1st International Standard for parvovirus B19 DNA. The study took place between September and November 2007 and the final report was prepared by Dr Sally Baylis at NIBSC. The study re-evaluated a freeze-dried plasma preparation containing B19V that was prepared from the same original bulk as the 1st IS. Stability studies were also performed on the replacement material using accelerated thermal degradation samples. Excellent stability was demonstrated for the candidate replacement IS. The results determined by the PEI were in good agreement with the other participating laboratories and the final report has been submitted to ECBS for review at the meeting in October 2008.

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

3.1 Trainee from the Department of Medical Sciences (DMSc), Ministry of Public Health, Thailand visit to the PEI WHO Collaborating Centre (CC), September 2007

An employee from the Thai Ministry of Health spent three weeks at the PEI CC in September 2007.

The Thai colleague visited the PEI CC

- Division 7, Sections 7/1, 7/2, 7/3: Coagulation Products I (head: Dr Anneliese Hilger) and II (head: Dr Johannes Dodt), and Batch Release, Blood Products, Logistics (head: Dr Uwe Unkelbach);
- PEI-IVD Testing Laboratory (head: Dr Sigrid Nick)

as well Division 5, Allergology.

3.2 Trainees from the Refik Saydam Hifzissihha Hygiene Center, Ankara, Turkey visit to the PEI WHO Collaborating Centre, January 2008

Three colleagues from the Refik Saydam Hifzissihha Hygiene Center visited the PEI-IVD Testing Laboratory in January 2008 to become familiar with European procedures for CE marking of IVDs.

4. Other WHO Meetings, related to PEI CC activities

4.1 WHO/ISTH (International Society on Thrombosis and Haemostasis) Liaison Group Meeting, Vienna, Austria, 3 July 2008

The meeting of the WHO/ISTH Liaison Group took place in Vienna as part of the ISTH SSC (Standardisation and Scientific Committee) Meeting. The meeting was chaired by the ISTH liaison officer, Professor Koen Mertens. Further participants were the chair of the SSC, the chair and a further member of the ISTH Council, the ISTH Executive Director, and WHO CCs related to blood: NIBSC, FDA/CBER, and the PEI, which was represented by Professor Seitz.

The Liaison Group endorsed standard preparations, which had been peer reviewed by recognized SSC experts. Three proposals were forwarded to the WHO ECBS for adoption: the 4th IS for Factor IX in Concentrate, 2nd IS for Factor VIIa in Concentrate, and Genetic Reference Material for Haemophilia A, intron 22 inversion. Ongoing work and several proposals for new standardization projects were also discussed. This included for example, the ongoing replacement of the 7th IS for Factor VIII in Concentrate, taking into account that different assays are used in different regions (chromogenic assay in Europe according to the relevant PhEur monograph, one-stage clotting assay in the USA), and that discrepancies between plasma derivatives and recombinant products have been observed. This issue has already been discussed in the BRN, and will need further attention.

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

5.1 15th IPFA/PEI NAT Workshop on Surveillance and Screening of Blood Borne Pathogens, Vienna, Austria, 13 – 15 May 2008

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 Vienna was the first one which was not in direct conjunction with SoGAT (now only every two years). Nevertheless, it attracted around 200 attendees who participated in this three days congress. Dr Baylis of PEI gave a presentation on the standardization efforts for B19V NAT. This included the study to replace the WHO International Standard, results from the EDQM proficiency testing scheme for 2007 and progress in the establishment of a B19V genotype panel. Dr Johannes Blümel, PEI, introduced different safety models on the field of B19V contamination of plasma derivatives, and Dr Nübling participated in the final panel discussion summing-up the different topics of this successful congress. The next IPFA / PEI workshop will be held on 26 – 27 May 2009 in Brussels, Belgium.

5.2 SoGAT (Standardization of Gene Amplification Techniques) – Clinical Virology (1st meeting at NIBSC, UK, 24 – 25 June 2008)

After the successful experience of the SoGAT approach for the standardization of blood screening NATs (e.g. by design and manufacture of WHO International Standards for the different screening targets) there has been a demand from different parties to extend this approach into the field of clinical microbiology. Dr Nübling attended the start-up SoGAT – Clinical Microbiology meeting which focused again on the NAT standardization. The meeting was held at NIBSC with quite different topics mainly from the clinical virology field, but also from clinical bacteriology and parasitology. The meeting was attended by more than 40 participants representing the different fields and coming from many countries worldwide. Dr Nübling gave two presentations to describe the experience from previous SoGAT on blood screening targets to the new audience. After two days there was common agreement that this new kind of SoGAT meetings should be continued. The SoGAT meetings on blood screening NAT will be continued, too, and are now organized every two years in conjunction with the IPFA (International Plasma Fractionation Association) / PEI workshops. The next meeting for the blood screening NAT will take place in Brussels in May 2009.

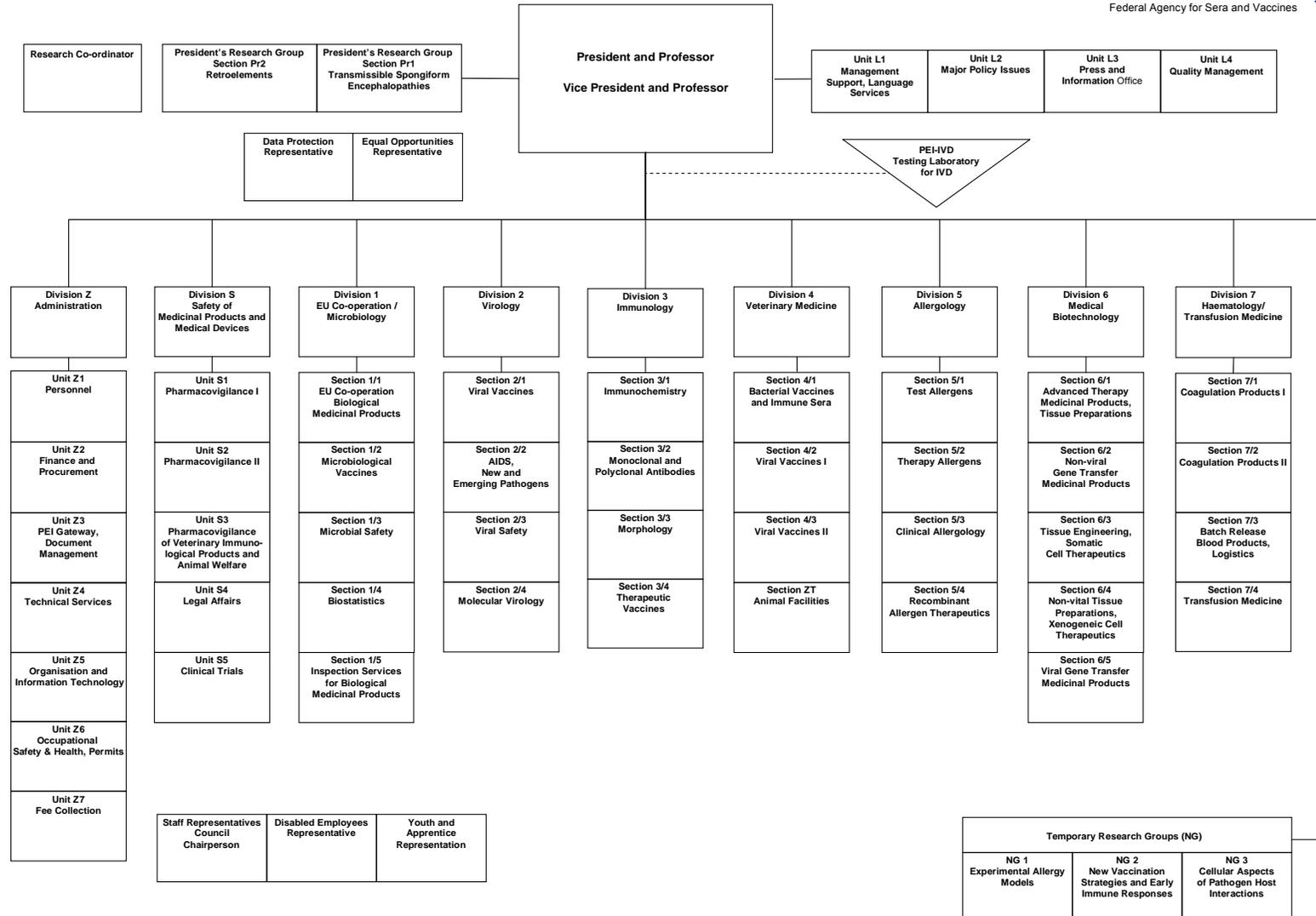
Current list of professional staff of the WHO Collaborating Centre

- 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;
- Dr Gabriele Unger, coordinator of the Collaborating Centre (Training of Assessors programme; PEI Unit L3, Public Relations);

In alphabetical order:

- Dr Sally Baylis (project leader Parvovirus B19 Genotype Panel; PEI Section 2/3, Viral Safety);
- 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);
- 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 (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 Reference Panel; head of PEI Section 2/4, Molecular Virology);
- Dr Heinrich Scheiblaue (secondment to WHO/HSS/PSM/QSD from April 2008 until March 2009; 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 Uwe Unkelbach (head of PEI Section 7/3, Batch Release, Blood Products, Logistics);
- Ms Sabine Heinz (head of PEI Section 1/5, Inspection Services for Biological Medicinal Products).

Paul - Ehrlich - Institut Organizational Chart



As of 1 April 2007

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¹ PEI co-workers in bold print

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Press Release on occasion of the World Health Day on 7 April 2008

WHO dedicated the World Health Day 2008 to its 60 anniversary and focused on the protection of health influenced by climate change. The Paul-Ehrlich-Institut published a press release in order to support the global efforts of encountering the upcoming challenges for health. The institute focused on the outspread of infectious diseases due to climate change and also growing mobility of people.

The press release was published in German.

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Weltgesundheitstag: enge Zusammenarbeit des Paul-Ehrlich-Instituts mit der WHO

Der diesjährige Weltgesundheitstag steht unter dem Motto: "Vom Seuchenschutz bis zum Klimawandel – 60 Jahre WHO". Ein wichtiges Standbein des Seuchenschutzes ist der Impfschutz. Und gerne wird vergessen, welche Anstrengungen nötig waren, um Infektionen wie HIV und Hepatitis B und C durch Blut und Blutprodukte zu verhindern. Insbesondere in weniger entwickelten Ländern stellt diese Gefahr nach wie vor ein Problem dar, an dessen Lösung die WHO aktiv arbeitet. Das Paul-Ehrlich-Institut in Langen, zuständig u.a. für die Zulassung von Impfstoffen und Blutprodukten, unterstützt seit langem die WHO in diesen Bereichen.

Klimawandel und Globalisierung

"Neuerdings wird befürchtet, dass der Klimawandel die Ausbreitung von bisher exotischen Infektionserregern durch Stechmücken auch in unsere Zonen begünstigt. Wir im Paul-Ehrlich-Institut helfen mit, zuverlässige Testverfahren zu etablieren, die auch in der Zusammenarbeit mit der WHO genutzt werden können", so Johannes Löwer, der Präsident des Paul-Ehrlich-Instituts.

Aber nicht nur Stechmücken wandern umher. Auch Urlauber und in zunehmendem Maße Geschäftsreisende und Arbeitnehmer halten sich immer häufiger für längere Zeit in weniger entwickelten Ländern auf. "Daher ist das Ziel, die Häufigkeit von Infektionskrankheiten (Prävalenz) vor Ort zu vermindern auch für unsere Bevölkerung sehr wichtig. Ebenso sollen diese Länder zunehmend mit sicheren und wirksamen

Impfstoffen und Blutprodukten versorgt werden können", so Löwer. Dabei bleibt das Paul-Ehrlich-Institut ein wichtiger Kooperationspartner der WHO.

Zusatzinformationen zur Arbeit des PEI im Hinblick auf Impfstoffe und Blutprodukte

Seit Jahrzehnten überprüft das Paul-Ehrlich-Institut die Qualität und Sicherheit von Impfstoffen und Blutprodukten für Deutschland und Europa.

Impfstoffe

Im Mittelpunkt der Zusammenarbeit mit der WHO stehen derzeit natürlich die Planungen und Vorbereitungen einer möglichen Influenzapandemie. Seit 2006 nimmt das PEI auch am "UN Prequalification Programme for Vaccines" teil, das von der WHO organisiert wird. Hierbei prüfen Experten des Instituts Unterlagen über Impfstoffe, die von den Vereinten Nationen für Entwicklungsländer gekauft werden sollen, und testen Impfstoffe in den institutseigenen Labors. Sollten, wie von vielen befürchtet wird, durch den Klimawandel neue Erreger und in der Folge neue Impfstoffe nach Europa bzw. Deutschland kommen, so wird das Institut seine Zusammenarbeit mit der WHO entsprechend ausweiten.

Blutprodukte und zugeordnete In-vitro-Diagnostika

Die Expertise des Paul-Ehrlich-Instituts bei der Überprüfung dieser Produkte ist weltweit anerkannt. 2005 wurde das Institut deshalb von der WHO zum "WHO Kooperationszentrum für die Qualität von Blutprodukten und In-vitro-Diagnostika" ernannt (WHO Collaborating Centre for the Quality Assurance of Blood Products and in vitro Diagnostic Devices).

In vielen Entwicklungsländern gibt es noch immer große Lücken in der Blutversorgung. Das Fehlen von Bluttransfusionen ist einer der wesentlichen Gründe für die hohe Sterblichkeit von Frauen bei der Geburt (perinatal) und auch von Neugeborenen. Fehlender Blutersatz ist ebenfalls eine Ursache für die Sterblichkeit von Kleinkindern nach Erkrankung an Malaria.

Ist Blut vorhanden, wird oft gar nicht oder nur eingeschränkt auf die wichtigen Infektionserreger getestet (HIV, Hepatitis B und C). Weltweit geht die WHO pro Jahr von rund 81 Millionen Blutspenden in 178 Ländern aus. Die entsprechenden Tests auf Infektionserreger entsprechen nach WHO-Schätzungen aber nur in etwa 65 Prozent der Fälle internationalen Qualitätsstandards. 28 Millionen Blutspenden jährlich werden demnach weltweit gar nicht oder nicht ausreichend getestet (s. "WHO Global Database, Bericht 2001 – 2002"). Das PEI setzt sich in seiner Zusammenarbeit mit der WHO intensiv dafür ein, die Blutversorgung und die Qualität von Blut und Diagnostika zum Nachweis von Infektionserregern zu verbessern.