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Name of the University, Hospital, Research Institute, Academy or Ministry
Paul-Ehrlich-Institute (PEI)
Name of the Division, Department, Unit, Section or Area
Division of Haematology and Transfusion Medicine

City	Langen	Reference Number	DEU-117
Title	WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices		
Report Year	07/2011 to 07/2012		

1. Please briefly describe the progress made in the implementation of your agreed workplan as WHO collaborating centre during the past 12 months (or the reporting period listed above). Please report on how each workplan activity was implemented, if any outputs have been delivered, if any results have been achieved and if any difficulties have been encountered during this time. If an activity has previously been completed, has not started yet, or been placed on hold, please indicate this.

Activity 1

Title: Development of International Reference Panel for Parvovirus B19 Genotypes for Nucleic Acid Amplification Technique (NAT)-Based assays
Description: A plasma panel has been prepared representing the main genotypes of parvovirus B19. The study has involved the participation of all three WHO Collaborating Centres for Biological Standards and Standardization. A collaborative study has been performed involving 34 laboratories worldwide where the genotype panel has been evaluated in parallel with the 2nd WHO International Standard for parvovirus B19 DNA for NAT-based assays.

The 1st International Reference Panel for B19V Genotypes was adopted by the Expert Committee on Biological Standardization (ECBS) in October 2009 (WHO/BS/09.2122). The panel was developed in collaboration involving the PEI, the Center for Biologics Evaluation and Research (CBER)/ Food and Drug Administration (FDA) USA and the National Institute for Biological Standards and Control (NIBSC) UK. The panels are available from CBER/FDA and NIBSC (CBER Parvovirus B19 Genotype Panel 1, NIBSC code number 09/110, respectively).

Baylis SA, Ma L, Padley DJ, Heath AB, Yu MW; Collaborative Study Group. Collaborative study to establish a World Health Organization International genotype panel for parvovirus B19 DNA nucleic acid amplification technology (NAT)-based assays. Vox Sang. 2012;102:204-11.

Activity 2

Title: Development of an International Standard for Hepatitis E Virus RNA for Nucleic Acid Amplification Technique (NAT)-based assays
Description: Initially it is proposed to prepare a small proficiency panel to evaluate laboratory performance for the detection of HEV RNA. The participants of this study should include reference laboratories for viral hepatitis, public health laboratories, blood banks/plasma fractionation organizations, control laboratories, research laboratories and organizations developing vaccines and IVD manufacturers developing HEV NAT assays. After this initial pilot study, it is proposed to prepare an International Standard for HEV RNA. Four genotypes of HEV are known to infect man. Types 1 and 2 are restricted to humans, whilst genotypes 3 and 4 infect other hosts such as pigs, wild boar and deer. Zoonotic infection of genotypes 3 and 4 occur in man and strains of these particular genotypes have been shown to be transmitted by transfusion. A genotype panel would be particularly useful however genotype 3 strains will be used initially to develop an International Standard due to the availability of sufficient volumes of plasma and their detection worldwide.

Hepatitis E virus (HEV) is a major public health concern, responsible outbreaks of acute viral hepatitis cases in endemic areas (e.g. in Africa, Asia, Central America). High mortality rates of up to 25% occur in pregnant women and individuals with underlying liver disease. In industrialized countries HEV infection may be linked to travel to endemic areas, however autochthonous cases are increasing, with zoonotic transmission from swine and other species. HEV viraemia and faecal shedding occur several weeks prior to the development of anti- HEV IgM and IgG. It is now recognized that HEV diagnostic testing, including NAT, is important in patients where other causes of acute hepatitis have been excluded. Transfusion transmission of HEV occurs and the virus is relatively resistant to viral inactivation/removal procedures, consequently NAT screening has been proposed for certain classes of plasma-derived products with limited virus reduction steps. Vaccines against HEVhave been developed. Astandard was required for detection/quantification of HEV RNA for use in clinical laboratories, particularly hepatitis reference laboratories, as well as blood banks, plasma fractionation organizations and associated control laboratories.

An initial study was performed to evaluate a panel of hepatitis E virus (HEV) containing plasma samples to determine a suitable strain to develop into a WHO IS and to investigate performance of HEV RNA NAT-based assays. The panel comprised 22 HEV positive plasma samples representing ten-fold serial dilutions of genotypes 3a, 3b, 3f and 4c. Two HEV negative plasma controls were included in the panel. All samples were blinded. The plasma samples were prepared as liquid frozen materials which were distributed to participants on dry ice. Laboratories were requested to test the panel using their routine HEV assays and score samples as either positive or negative. Where quantitative assays were available laboratories were encouraged to return data in copies/ml for HEV RNA. Twenty laboratories from 10 different countries participated in the study. Data sets were returned from 24 different assays, with 10 laboratories returning quantitative data from one or more assays. All assays, except one, were developed in-house and included conventional as well as real-time RT-PCR methodologies. There was a 100- to 1000-fold difference in sensitivity between the majority of assays, independent of the virus strain. No single HEV strain of either genotype was consistently detected or quantified more readily than any of the others, and it was proposed to develop the genotype 3a strain as the candidate International Standard and the genotype 3b strain as the candidate Japanese national standard. The candidate standards were lyophilized in August 2010 and the collaborative study was performed in conjunction with the Japanese National Institute for Infectious Diseases (NIID).

For the subsequent collaborative study, coded duplicate samples of the two strains were distributed to participating laboratories; genotype 3a HEV (Samples 1 and 2) and genotype 3b HEV (Samples 3 and 4). The samples were assayed on 4 separate occasions and the data were collated and analysed at the PEI. The study involved 23 laboratories from 10 countries. All assays were able to detect both candidate standards. The combined mean estimates for the 2 candidate standards were 5.60 log10 copies/ml (quantitative NAT) and 5.26 and 5.29 log10 NAT-detectable units (qualitative NAT - end-points), respectively.. Based upon the combined data, the preparations were estimated to have a potency of 5.39 log10 units/ml. Since the unitage assigned to the 1st WHO standard of a preparation is essentially arbitrary, for practical purposes, the candidate International Standard was assigned a unitage of 250,000 International Units/ml. Since there was only a negligible difference in the overall means for the candidate Japanese National Standard compared to the WHO preparation, the two materials were therefore been assigned the same value i.e. 250,000 International Units/ml. Sample 1/2 (PEI code number 6329/10) was established as the 1st International Standard for hepatitis E virus RNA by the WHO Expert Committee on Biological Standardization (ECBS) at the annual meeting in Geneva in October 2011.

Baylis SA, Hanschmann KM, Blümel J, Nübling CM; HEV Collaborative Study Group. Standardization of hepatitis E virus (HEV) nucleic acid amplification technique-based assays: an initial study to evaluate a panel of HEV strains and investigate laboratory performance. J Clin Microbiol. 2011;49:1234-9.

Activity 3

Title: Transfusion-Relevant Bacterial Strain Panel
Description: The panel members are bacterial strains selected for their ability to replicate in blood platelet concentrates (PCs) under routine storage conditions used in transfusion medicine. They are prepared using a specially developed procedure which guarantees defined bacterial suspensions (deep frozen, ready to use, stable, shippable, defined in count of living cells). The panel is designed to allow objective validation of methods for bacterial screening as well as technologies for pathogen reduction in PCs under "real life" conditions, i.e. inoculating the PCs with a very low bacteria count (0.03 to 0.3 CFU/ml) followed by growth in the matrix.

Bacterial contamination of platelet concentrates (PCs) still remains a persistent problem in transfusion. To mitigate the risk of bacterial contamination of blood components, blood centres have implemented bacterial detection systems or pathogen reduction technologies (PRT). In order to validate and to compare these methods, it is crucial to use bacterial strains which are able to proliferate in blood components. Bacteria may proliferate in PCs during storage, but bacterial contamination of blood components will not always result in bacterial multiplication.

Previously, no international bacterial references existed in order to perform low titre spiking experiments for the objective validation and comparison of bacteria detection methods and PRT. Therefore, the International Society of Blood Transfusion (ISBT) Working Party Transfusion-Transmitted Infectious Diseases (WP-TTID, chair: Dr Silvano Wendel), Subgroup on Bacteria (chair: Dr Thomas Montag-Lessing), organized an international study on Transfusion-Relevant Bacteria References (TRBR) to be used as a tool for development, validation and comparison of both bacterial screening and pathogen reduction methods.

Four TRBR were blinded and distributed to 14 laboratories in 10 countries for identification, enumeration and proliferation analyses in PCs after low titre spiking (0.3 and 0.03 CFU/ml). Thirteen laboratories returned data concerning bacterial counts and identity; twelve laboratories returned data on the growth ability of the strains. The results of the study demonstrated the stability of the TRBRs and consistency of results in a large number of transfusion laboratories worldwide.

In 2010, the ECBS approved the proposal to establish the first WHO Repository for Transfusion-Relevant Bacteria Reference Strains. The repository consists of four bacteria strains which were included in the international collaborative study (i.e. Staphylococcus epidermidis (PEI-B-06), Klebsiella pneumonia (PEI-B-08), Streptococcus pyogenes (PEI-B-20), and Escherichia coli (PEI-B-19)) and these are maintained and distributed by the Paul-Ehrlich-Institut (PEI). The committee requested detailed instructions for use, which were provided by PEI in February, 2011.

The ECBS also endorsed a proposal for the addition of further bacterial strains to the WHO Repository. A total of 10 different bacteria preparations, suitable for the control of platelet concentrate contamination, will be available. Appropriate characterization will need to be performed in an international collaborative study, and this was discussed during the annual subgroup meeting of WP-TTID, Subgroup on Bacteria, during the 21st Regional Congress of the International Society of Blood Transfusion, Lisbon, Portugal in June 2011, as well as during the extraordinary meeting WP-TTID, Subgroup on Bacteria, in San Diego, California, in October 2011.

9 candidate bacterial strains as well as five isolates serving as alternatives are currently tested at the PEI for stability. Sequencing of bacterial 16srRNA will be performed, and these strains will be included in the expanded study and distributed to the participating laboratories for testing in platelet concentrates in Q4 2012.

The results of the first study were published in Vox Sanguinis in 2011 (Störmer et al., Establishment of the first International Repository for Transfusion-Relevant Bacteria Reference Strains ISBT Working Party Transfusion-Transmitted Infectious Diseases (WP-TTID), Subgroup on Bacteria; Vox Sanguinis, 2011 Jul. 7. doi: 10.1111/j.1423-0410.2011.01510.x.).

Activity 4

Title: Development of hepatitis B virus (HBV) genotype reference preparations for HBV DNA assays and HBsAg tests.
Description: The analytical sensitivity of HBV NAT assays and HBsAg tests is based on the respective WHO International Standard which represents genotype A2. The commutability in respect to the other HBV genotypes is an open issue. The establishment of WHO International Reference Panels representing different HBV genotypes was proposed by the Paul-Ehrlich-Institut. This proposal was endorsed by the WHO Expert Committee on Biological Standardization in 2005 as a high priority project. Around 215 potential candidate members representing HBV DNA/HBsAg high-titre plasma samples from all Regions were characterized. The final panels for NAT assays and for HBsAg tests comprise 15 members each representing the genotypes A to G and A to H, respectively. Twelve samples are common between both panels.

The proposed 1st International Reference Panel for HBV genotypes (PEI code number 5086/08), intended for use with HBV NAT assays, consists of 15 lyophilized HBV positive plasma samples which cover the most prevalent HBV genotypes A to G worldwide, was established by the ECBS in October 2009 (WHO/BS/09.2121). The panel is held at PEI and is available on request. The panel is ordered on a regular basis by control authorities, IVD manufacturers and users of HBV-NAT test kits. A manuscript on design, manufacture and characterization of the panel has been submitted to a peer-reviewed scientific journal.

The second part of the WHO project involved the development of an international reference panel for HBV genotypes designed for the use with hepatitis B surface antigen (HBsAg)-based diagnostic kits. This panel (PEI code number 6100/09) consists of 15 different members, which represent sub genotypes A1 (2), A2, B1, B2, C2 (3), D1, D2, D3, E, F2 (2), and H. The amount of infectious virus particles in the HBV positive plasma samples was significantly reduced by an ultracentrifugation step prior to dilution and lyophilization of the panel members. This step resulted in a virus removal of > 97 %, with the exception of Sample 14 (80 % elimination) and Sample 10 without ultracentrifugation due to the limited volume. The determination of HBsAg concentration by three different methodologies (chemiluminescent immunoassay (CLIA), quantitative immuno electrophoresis (QIE) and antigen purification) demonstrated that the corresponding different reported HBsAg unitages, international unit (IU), Paul-Ehrlich-Institut unit (PEI-U) and nanogram (ng), respectively, yielded similar results for most of the HBV genotype samples, but the differences for some samples, caused by technical limitations, exceeded the standard deviation. Residual water content in the final vials containing lyophilized plasma was determined as 0.70 ± 0.11 %, again predicting long-term stability at the recommended storage condition (-20°C or below) of the panel. On-going real-time stability studies are in progress. The aim of the collaborative study was to evaluate the panel of lyophilized samples containing different HBV sub genotypes for its use with HBsAg-based diagnostic assays. Each laboratory analysed the panel samples in parallel to the 2nd WHO International Standard (IS) for HBsAg (NIBSC code 00/588) representing HBV sub genotype A2. Participants performed three independent runs. The data were collated and the statistical analysis performed at PEI. In total, 22 qualitative data sets (18 different HBsAg tests) and six quantitative data sets (two different HBsAg tests) from 14 participants were used in the evaluation. Overall, the results demonstrated quite consistent detection of HBV genotypes A-F and H by the majority of the test kits investigated, with few assays showing genotype-dependent effects on detection efficiency. Based on the results of the collaborative study, it is proposed that the panel should be established as the 1st International Reference Panel for HBV Genotypes for HBsAg-based assays (PEI code number 6100/09). No unitage is assigned to the individual panel members. However, the statistical data determined for each panel member from the collaborative study will be provided. The panel will be helpful for manufacturers as well as users of in vitro diagnostic devices to check the relative detection efficiency of HBsAg diagnostic test kits in relation to different HBV genotypes. Furthermore it will support regulatory authorities in the assessment of HBsAg assays for the detection of HBsAg in relation HBV genotypes prevalent in their regions. The project was presented at the ECBS meeting in October 2011 and the panel was adopted by ECBS as 1st WHO International Reference Panel for HBsAg Genotypes.

Activity 5

Title: Establishment of the 1st International Standard for Hepatitis D Virus RNA
Description: For the preparation of the standard material HDV RNA-positive plasma samples representing the most predominant clade HDV-1 will be provided by the Institute of Hepatology, Ankara University, Turkey. A feasibility study will be performed involving several laboratories worldwide to evaluate the reference material. If the characterization of the candidate materials reveals suitable antibody titres, it will also be possible to establish an international anti-HDV antibody standard material.

The hepatitis D virus (HDV) is a defective 1678 nucleotide single-stranded RNA virus that requires the helper function of hepatitis B virus to replicate. HDV genotype 1 (HDV-1) is the most predominant worldwide, and is associated with a broad spectrum of chronic HDV disease. Co- and super infections with HBV-dependent HDV can lead to serious complications, such as fulminant acute hepatitis or severe chronic active hepatitis, often progressing to cirrhosis. Chronic HDV infection may also lead to the development of hepatocellular carcinoma. Since no effective antiviral therapy is currently available for treatment, liver transplantation may be considered for fulminant acute cases and end-stage chronic HDV. Administration of alpha-IFN (interferon) may help to improve the condition. Nowadays, the NAT assays are the method of choice for the diagnosis of ongoing HDV infection and monitoring treatment. Monitoring HDV viraemia following treatment with pegylated IFN by quantitative real-time polymerase chain reaction (PCR) is state of the art. Currently only a few commercial HDV NAT assays are available on the market. Most NAT assays used have been developed in-house and are not well standardized and are therefore difficult to compare. This may cause problems in the treatment of chronic hepatitis D. International reference material is urgently required to standardize the NAT tests. Furthermore, the comparison of standardized NAT results will facilitate new strategies for successful treatment. The PEI proposed the development of an international standard for HDV RNA (genotype 1). The proposal was endorsed by the WHO ECBS in October 2009. The project is being undertaken in close cooperation with the Institute of Hepatology, Ankara University, Turkey and with the Institute for Medical Virology, Justus von Liebig University in Giessen, Germany. One of the outcomes/needs from the EASL (European Association for the Study of the Liver) Monothematic Conference Delta Hepatitis held in Istanbul, Turkey in September 2010 were that EASL strongly support the standardization efforts. The type of standard proposed (i.e. HDV diluted in human plasma, analogous to the other WHO NAT standards for blood borne viruses) would be suitable for all current NAT methods. The proposed standard preparation will consist of 2000 – 4000 vials containing approximately 105 copies HDV-RNA/vial. The fill volume is 0.5 ml per vial. A pilot study was initiated in June 2012 to show feasibility of HDV-RNA detection and quantification; dependant on the initial results obtained in this pilot study, the protocol will be elaborated in order to further evaluate the candidate WHO IS. If the outcome is successful, the final report is expected to be submitted to the ECBS in July 2013 for establishment of the 1st International Standard for HDV RNA.

Activity 6

Title: Preparatory work with the aim to establish the 1st International Standard for factor XIII concentrate
Description: An IS for factor XIII in plasma has been established successfully, with values assigned for both activity and antigen. The potency assay of factor XIII concentrate turned out to be problematic, since the matrices found in products lead to different behaviour in existing assays. The problem is dealt with by the factor XIII standardization working party (FXIIISWP) of the ISTH SSC subcommittee on fibrinogen and factor XIII (co-chair: Professor Seitz). This working group is currently collecting materials (samples of different factor XIII concentrates, reagents) and drafting protocols for studies aiming at identifying a strategy for establishing the 1st IS for factor XIII concentrate, with assigned values for activity and antigen.

This project was devised by the ISTH SSC (International Society on Thrombosis & Haemostasis/ Scientific and Standardization Committee) Working Party on Factor XIII Standardization (Chair: Prof. Akitada Ichinose, Yamagata University, Japan). During the ISTH SSC Meetings in Kyoto 2011, it was decided to discontinue Working Parties and to run projects under the control of the respective subcommittees instead. The group met in February 2012 during the GTH congress in St. Gallen to discuss this new development. Initial priority was given to a project to develop an assay for factor XIII subunit B, in view of the upcoming recombinant Factor XIII product which contains only subunit A and should be given only to patients with sufficient subunit B level. The PEI continues to be interested in establishing the 1st International Standard for factor XIII concentrate, however this project is currently on hold.

Activity 7

Title: Exploration of a new factor VIII potency assay
Description: Discrepancies occur between potency values obtained with the two current methods (the chromogenic and the one-stage assay), particularly with immunopurified FVIII and recombinant products. It is not clear which assay better reflects clinical efficacy. A new and better assay is needed to reflect clinical effectiveness. Thrombin generation is a possibility, PEI is working on a modification, a fluorogenic assay using FIXa as trigger and FXa as read-out.

There are discrepancies between results of the chromogenic and the one-stage clotting potency assays which appear most pronounced when FVIII activity is measured in immune-purified Factor VIII (FVIII) and B-domain deleted products.

The one-stage clotting assays are used for clinical purposes and product labelling e.g. in the USA. However, the European Pharmacopoeia (Ph. Eur.) prescribes the chromogenic assay for potency determination, and anticipates that in the case of recombinant FVIIIs, product-based reference materials, the activity of which is determined relative to the international standard, will be used.

Problems due to discrepancies found with different assays are expected to become even more pronounced with novel modified products. This issue was discussed during the Second WHO Collaborating Centres Meeting held at PEI in February 2009.

Haemophilia treatment is to a great extent empirical. Clinical studies establishing a relation between dosage of individual therapeutic products and clinical efficacy are missing; the treatment follows in essence general recommendations on target FVIII levels in certain clinical circumstances. Crucial for pre-licensing clinical evaluation of therapeutic products is a pharmacokinetic study, where the FVIII level is assessed in a number of patients at fixed time points after injection. In clinical practice, products are usually dosed according to labeled potency, the measurement of resulting FVIII plasma levels is crucial for monitoring therapy in hemophilia A patients. Thus, there should be a link between the labeled potency of a product and the FVIII levels measured in the patients´ plasma. Confronted with discrepancies between the values obtained with different potency assays, the question arises which of the assays would best reflect the desired clinical effect, i.e. control of bleeding. However, this question has not been answered by clinical studies, and it is difficult to answer on theoretical grounds.

PEI experts continue to work in advisory groups including the Ph. Eur. expert group 6B, the EMA Biologics Working Party, and committees in scientific societies, e.g. the International Society on Thrombosis & Haemostasis (ISTH) in order to explore possibilities to optimize existing test methodology as well as new alternatives, with the aim to harmonize FVIII potency measurement in a way suitable for both clinical and regulatory purposes. In particular, Drs. Dodt and Seitz took part in the SSC/ISTH Factor VIII / Factor IX Sub-committee Project on the Potency of Clotting Factor Concentrates, which developed a document, entitled "RECOMMENDATIONS ON THE POTENCY LABELLING OF FACTOR VIII AND FACTOR IX CONCENTRATES" (http://www.isth.org/default/assets/File/SSC/Subcommittees/POTENCY_LABELLING_RECOMMENDATIONS_DRAFT2.pdf).

Activity 8

Title: Participation in collaborative studies to establish the 2nd International Standard (IS) for von Willebrand factor (VWF) concentrate.
Description: In the past years, VWF concentrates have been licensed beyond Europe, e.g. in the USA. The potency assay for VWF turned out to be particularly problematic. The 1st IS for VWF concentrate improved the situation, but it was not possible to assign a value for the collagen binding assay, due to discrepancies encountered with the use of different reagents and methods. Also with the ristocetin cofactor assay, discrepant results occurred. Further analysis of data and possibly further laboratory work will be needed.

PEI participated in the collaborative study to establish the 2nd International Standard (IS) for von Willebrand factor (vWF) concentrate (the 1st IS was established in 2001; WHO/BS/01.1947). The project has been coordinated by NIBSC, UK. The main aim in the study was to assign potencies to the VWF:antigen and VWF:ristocetin cofactor and a new analyte, VWF:collagen binding, by assay relative to the WHO 1st IS and the WHO 6th IS Factor VIII/VWF, plasma. These analytes are all represented in a single preparation (NIBSC code number 09/182). The final decision for the assignment of the potency was made during the ECBS meeting in October 2010. The concentrate was adopted and is available from NIBSC, code number 09/182.

Activity 9

Title: Active participation in the initiative: "Assuring safety and availability of blood products in developing countries: Good Manufacturing Practices (GMP) & Educational Tools for blood/plasma collection establishments"
Description: Dr Gerd Werner has been seconded from the PEI to the WHO Headquarters in Genea, in order to support WHO activities in the field of GMP in blood establishments. PEI considers of high priority the WHO initiative to establish and implement a WHO guideline on GMP for blood establishments and to organize meetings and training courses in several regions of the world, with presentations by experienced inspectors (including PEI), and attendance of pharmaceutical inspectors, heads of blood national programs and delegates from regulatory authorities in the respective regions

An important part of the initiative was the drafting of the WHO Guideline on Good Manufacturing Practice (GMP) for Blood Establishments (WHO/BS/10.2139) (see also Activity 12). After extensive discussions and work on the guideline it was finally adopted by the Expert Committee on Biological Standardization (ECBS) in October 2010.
No further activities were carried out during the reporting period.

Activity 10

Title: Participation in the Blood Regulators Network (BRN)
Description: The BRN is a working group of six leading regulatory authorities in the field of blood products with the task of reacting rapidly to emerging risks, assessing new technologies, and providing advice to WHO. Professor Seitz had been the first chairperson of the BRN (2006 to 2008). Current topics are e.g. preparedness for pandemic, impact of storage of red cells on outcome of transfusions, pathogen inactivation technology.

The WHO Blood Regulators Network (BRN), established following a recommendation of the 11th International Conference on Drug Regulatory Authorities (ICDRA, Madrid, Spain, 16 – 19 February 2004), has been operating since 2006.

According to its Terms of Reference, 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). Responding to critical situations in a fast and flexible way is particularly important.

The BRN work focuses on:
•scientific assessment of current and emerging threats to the safety and availability of blood and blood products;
•scientific assessment of the impact (i.e. potential benefits and drawbacks) of new technologies;
•exploration of opportunities among regulatory authorities to cooperatively address emerging public health challenges;
•exploration of opportunities for regulatory collaboration/ harmonization.

The BRN reports to the ECBS and assembles at least annually during the regular ECBS meeting at WHO headquarters in Geneva. In 2011, this meeting took place on the 20th of October. Furthermore, BRN telephone conferences were held on 16th of June, 7th of September, 11th of October, and 11th of November 2011, and on 3rd of February, and 5th of March 2012.

During the face-to-face meeting on 22 October 2009, a representative of Ministry of Health of Japan was present and explained the Japanese interest in participating in the BRN. Since the current BRN Terms of Reference did not allow inclusion of new Members, the BRN decided to propose amendments of the Terms of Reference, which were finally adopted by the ECBS and WHO Secretariat. At the meeting on 20th of October 2011, the BRN welcomed the new colleagues representing the Japanese Ministry of Health, Labour and Welfare (MHLW), a newly established Member of the BRN. Thus, the BRN comprises now seven regulatory authorities (referred to as "Members") which have comprehensive responsibility for the regulation of blood, blood products and related IVDs, and possess the necessary expertise and capacity to address emerging public health challenges. The other Members are (in alphabetical order of country): Therapeutic Goods Administration (TGA), Australia; Health Canada, Canada; Agence nationale de sécurité du médicament et des produits de santé (ANSM), France; Paul-Ehrlich-Institut (PEI), Germany; Food and Drug Administration (FDA), USA, and Swissmedic, Switzerland. Each authority is represented by a member and an alternative member. The PEI representatives are Professor Rainer Seitz, who served for two years (2006 to 2008) as the first BRN chairperson, and Dr Margarethe Heiden. At the meeting on 20th of October 2011, Dr Peter Ganz (Health Canada) was elected as new BRN chair for a term of two years.

A major focus of the BRN in the past year was the finalisation of Assessment Criteria for Evaluation of Blood Regulatory Systems. This project had been proposed by the Canadian colleagues during the BRN meeting in Ottawa in March 2008, and Health Canada and Swissmedic took the lead in developing draft documents, and evaluated them in a self-assessment exercise. The project is expected to be an important contribution to the implementation of the resolution WHA 63.12. After a global consultation process undertaken via the Regional Offices the comments received were discussed and the draft amended accordingly. Subsequent to the BRN meeting on 20th of October 2012, the ECBS endorsed WHO adoption of the Assessment Criteria subject to final revisions.

The actual items of discussion, and the minutes of BRN meetings and teleconferences are confidential. However, general information about the BRN and documents produced by the BRN for publication are available on the BRN web site http://www.who.int/bloodproducts/brn/en/.

Activity 11

Title: Offer of Training courses for assessors working in regulatory authorities
Description: Courses conveying know-how by theoretical teaching and practical integration in ongoing activities of the PEI were initially designed for training colleagues from EC accession countries. The training courses have been developed and successfully implemented, and the scope has been broadened to be suitable for assessors from regulatory authorities from all over the world, including in particular developing countries. Since 2002, colleagues of regulatory authorities from various countries have taken part in the programme (number of trainees in brackets): Bulgaria, Estonia (2), Croatia (4), Lithuania, Romania, Czech Republic (4), Hungary, Turkey (13), Islamic Republic of Iran (7), Kuwait, Syria, Japan, Taiwan, Thailand (5), Vietnam (3). Trainees from Kuwait, Sudan and Syria were sponsored by the WHO/ EMRO fellowship programme. The training programme is organized as an array of modules, i.e. one to two weeks training units covering quality, non-clinical and clinical assessment, as well as laboratory control and batch release. The following modules relating to the WHO Collaborating Centre are available (responsible PEI experts in brackets):
a) Coagulation factors, albumin, and other blood products (Dr Uwe Unkelbach);
b) Immunoglobulins and immunosera (Dr Mueller-Berghaus, Dr Steffen Gross, Dr Siegfried Giess);
c) Viral safety of blood products (Dr Johannes Blümel);
d) Bacterial safety and pyrogen testing of blood products (Dr Thomas Montag-Lessing, Dr Ingo Spreitzer);
e) In vitro diagnostic devices for infectious markers and blood grouping reagents (Dr Micha Nübling, Dr Sigrid Nick);
f) Vigilance of in vitro diagnostic devices (Dr Markus Funk, Jochen Halbauer).
The courses are only available for employees from official (governmental) authorities who will be required to sign a confidentiality agreement .Training dates are arranged individually with the coordinator Dr Gabriele Unger. Trainees have free choice of modules, subject to availability of capacity (2 to 3 traineeships per module per year).

The training courses support the objectives of the WHO and the WHO Expert Committee on Biological Standardization (ECBS) to improve the regulation and control of blood products. This is also in line with the WHA Resolution 58.13 / Report EB113/10 and the WHA Resolution on Availability, Safety and Quality of Blood Products (WHA Resolution 63.12, adopted in 2009).

The PEI has extensive experience in the regulation of IVDs and blood products. The assessor training programme is used by medicines regulatory authorities and agencies worldwide.
The availability of WHO fellowships may assist in training costs.

11.1 Trainees from the Chinese National Institutes for Food and Drug Control (NIFDC), 29 Aug. – 15 Sept. 2011
Two colleagues from the NIFDC spent three weeks at the PEI visiting the Bacterial Safety section of the WHO Collaborating Centre.
The individual training programme contained the following contents:
"Bacterial safety and pyrogen testing"
•Sterility Control

oSterility testing of biologicals according to Ph. Eur. 2.6.1, demonstration of membrane filtration using Steritest container system (Millipore);

oSterility control of blood components, tissue preparations and cell therapeutics: theoretical introduction and discussion of specific problems regarding bacteriological safety of these products;

oAutomated computer controlled sterility testing, theoretical introduction: Ph. Eur. monograph 2.6.27 "Microbiological control of cellular products" and 5.1.6 "Alternative methods for control of microbiological quality",
principles of detection of bacterial growth in automated culture systems BacT/Alert 3D (Biomérieux) and BACTEC (Becton Dickinson);
practical demonstration of inoculation of Bact/Alert and BACTEC bottles (artificial contamination), loading, reporting and interpretation of data;

oAlternative methods for detection of bacteria in blood components, tissue preparations and cell therapeutics. Demonstration and practical application of rapid microbiological methods: growth based

method and early detection of colonies by fluorescence using Milliflex Quantum (Millipore); detection of bacterial contamination in eukaryotic cell suspension by flow cytometry using BactiFlow (AES Chemunex);

oDifferentiation and characterisation of bacteria by gram staining and API identification system.

•Pyrogen Testing

oPyrogen testing, Ph. Eur. 2.6.8 theoretical background;
followed by pre- and main test in routine batch control;

oBacterial endotoxin testing (LAL), Ph. Eur. 2.6.14 theoretical background; practical introduction to common (Gel-clot, chromogenic methods) and recently developed methods including rFc (recombinant Factor C) and PTS-System. Assessment of the current Perception of the BET by different Pharmacopoeias (Ph. Eur.; USP), the status of the horseshoe-crab populations worldwide and the putative consequences of insufficient supply with lysate.

oPyrogen testing by human whole blood assay
Thorough theoretical introduction into the field of alternative pyrogen testing in relation to rabbit pyrogen testing and BET.
Detailed description of method development, current situation (different MAT-versions; Ph. Eur. Monograph 2.6.30) of FDA; outlook to current and coming applications.
Practical training on MAT in routine batch testing (both fresh blood and cryoblood; Multi-Cytokine assay), evaluation of storage stability of cryoblood; detection of non-endotoxin pyrogens (NEP), intracellular cytokine detection by FACS.

11.2 Trainee from Health Sciences Authority (HSA), Singapore, 1 – 18 Nov. 2011
The colleague received the following training:
“Immunoglobulins, immunosera, monoclonal antibodies”
•Evaluation of polyclonal and monoclonal antibodies: Overview
•Case study Monoclonal antibody: XGEVA Solution for Injection 120mg/vial
•Case study for Ig VENA 50g/L Solution for infusion
•Testing of monoclonal antibodies: CAP test (Section 3/1)
•Licensing of immunoglobulins, immunosera, monoclonal antibodies
oNational procedure
oEuropean procedure (centralized)
oEuropean procedure (decentralized = mutual recognition)
•Relevant Guidelines
•Dossier evaluation: Presentation of a current assessment report
oQuality
?Immunoglobulins
?Monoclonal antibodies
•GMP-inspections
•Batch release
oOMCL system and general principle
oMeasures taken in case of defective batches
oCAP (Centrally Approved Products) Testing

“Coagulation factors, albumin and other blood products”
•Blood products (plasma derivatives) batch release
•Blood products (plasma derivatives) batch release
•Product audit on blood product
•General work flow/SOP
•Assessor’s role in product audit:
•CAPA and follow up

•Information
oEuropean network of Official Medicines Control Laboratories (OMCL)

oEU batch release procedure of blood products and medical devices
oNational batch release of blood products
oQM system

•Practical demonstration
oFVIII-chromogenic test
oAntithrombin – chromogenic test

“Quality of plasma derived and recombinant blood coagulation factors”
•European Pharmacopoeia requirements
oGeneral
oActivities regarding development of test methods, standards and monographs

•Licensing of coagulation factors
oNational Procedure
oDecentralized Procedure
oMutual Recognition Procedure
oCentralized Procedure

•Relevant Guidelines
oQuality
oPlasma Master File (PMF)

•Dossier evaluation: Presentation of a current assessment report
oDossier structure eCTD (EURS is Yours) and guidance on assessment of the quality part in general
oQuality Blood coagulation factors
Case study for von Willebrand Factor (Wilate 500 IU, 1000 IU) - Decentralized Licensing Procedure
oPlasma Master File

•GMP-inspections (assessor participation as product expert).

11.3 Visitors to the PEI WHO Collaborating Centre
Delegates from the Chinese State Food and Drug Administration (SFDA), the National Institutes for Food and Drug Control (NIFDC), the Chinese Pharmacopeia Commission, the Chinese Center for Pharmaceutical International Exchange (CCPIE) and several local authorities visited the Paul-Ehrlich-Institut in November 2011.
Clinical trial authorization of biological medicinal products and related ethical aspects in Germany were discussed with the Chinese visitors.

A delegation from the Korean Centers for Disease Control and Prevention (Korea CDC) and from the Korean Red Cross Blood Transfusion Research Institute visited the PEI on 18 July 2012 to discuss blood donor screening and hemovigilance systems.

Activity 12

Title: Contribution to the development of guidelines and recommendations
Description: The PEI has profound experience scientific and regulatory experience in the biological filed. PEI is also a leader regulatory authority in Europe and is actively involved in international scientific and regulatory committees. Experts of the PEI, as desired and appropriate, will be ready to actively contribute to the elaboration and/or updating of guidance documents, such as the guidance on blood products in Technical Report Series, No. 840.

As mentioned under Activity 10, PEI experts, as members of the BRN, contributed to drafting and elaborating of the document “Assessment Criteria for Evaluation of Blood Regulatory Systems”.

Activity 13

Title: Development of an International Hepatitis C virus (HCV) Core Antigen Standard
Description: A HCV core antigen standard would be especially useful for estimating the sensitivity of HCV core antigen assays and of HCV Ag/Ab combination assays. It may also serve for calibration of reference materials by manufacturers of diagnostic kits.

Hepatitis C Virus (HCV) is distributed worldwide and a major cause of acute and chronic liver disease, including cirrhosis and liver cancer. Globally, an estimated 170 million people are chronically infected with HCV, with 3 to 4 million new infections each year. A relatively high number of these people do not have access to appropriate HCV testing. The virus is highly variable and 6 major genotypes comprising numerous subtypes with distinct geographical distributions have been described. Highly sensitive HCV Ag/Ab combination assays as well as qualitative and quantitative assays for the detection of HCV core antigen have recently become available. The HCV core antigen assays in particular show a performance comparable to that of commercially available viral load assays and thus appear to be suitable for screening of blood donations and for monitoring the therapeutic efficacy of antiviral treatment. Therefore, HCV core antigen assays may represent a reasonable alternative to HCV-RNA detection and quantification and may contribute to the improvement of health and blood safety. An HCV core antigen reference preparation would be useful for the control of the quality of test kits by regulators and for standardization of HCV antigen quantification in routine clinical diagnostics. Manufacturers may use an HCV core reference material for the evaluation and development of improved HCV antigen detecting tests or new devices and for validation purposes. A proposal was presented in the WHO Collaborating Centers Meeting in February 2009 which was subsequently endorsed by the ECBS in 2009. The activities in 2011 and 2012 focused on the characterization of a high titer material available in sufficient quantities suitable for use in both HCV core and HCV Ag/Ab combination tests. The material originated from one US blood donor and is of HCV genotype 1, since this genotype shows a more broad geographical distribution. It was collected in 1996 and was drawn on two occasions, two days apart. In depth characterization of the material showed that it is suitable for both, highly sensitive HCV core assays and HCV Ag/Ab combination assays with lower sensitivity for HCV core. In the meantime, 1847 vials, each containing 0.5 ml of plasma have been lyophilized. . The lyophilized material has been demonstrated to maintain its reactivity in immunoassays. Currently three further high titer materials have been identified for inclusion in the collaborative study. Once the additional materials have been received, a collaborative study will be initiated to establish the International Standard.

2. Please briefly describe your collaboration with WHO in regards to the activities of the WHO collaborating centre during the past 12 months (e.g. means of communication, frequency of contact, visits to or from WHO). Please feel free to mention any difficulties encountered (if any) and to provide suggestions for increased or improved communication (if applicable).

2.1 62nd ECBS Meeting, Geneva, Switzerland, 17 - 21 October 2011
The Paul-Ehrlich-Institut is a WHO Collaborating Centre (CC) for Quality Assurance of Blood Products and in vitro Diagnostic Devices and as such its activities as closely linked to the ECBS. At the annual meeting of the ECBS, the president of the PEI, Professor Cichutek, described the recent activities of the WHO CC and the current work plan.
Professor Cichutek also summarized the further activities of PEI in connection with the WHO including the WHO Prequalification Programme for in vitro Diagnostics (see 2.4).

Dr Micha Nübling, rapporteur of the Blood Products Track of the ECBS meeting, also participated in the plenary session on the first day.
Dr Nübling made new proposals to establish International Standards for HBeAg, anti-HBe Ag as well as an International Reference Panel for HEV genotypes (HEV RNA). The ECBS committee members endorsed these proposals (see also 2.3). Furthermore he presented the project of Dr S. Baylis to establish a WHO IS for HEV-RNA which was later adopted by the committee.

Dr Michael Chudy presented the collaborative study performed for the candidate International Reference Panel for HBV genotypes (HBsAg). The project obtained a positive response and the panel was adopted.

2.2 New Projects endorsed at 62nd ECBS Meeting, Geneva, Switzerland, 17 - 21 October 2011

2.2.1 Development of a Hepatitis E Virus Genotype Panel
The 1st WHO International Standard for hepatitis E virus is a genotype 3a strain; the virus was obtained from Japanese blood donor. Whilst HEV is represented by a single serotype, the virus can be classified into at least four main genotypes. Genotypes 1 and 2 can be found in humans, particularly

causing large outbreaks of hepatitis E, whilst genotypes 3 and 4 are found in both humans as well as a range of animal species, particularly pigs and wild boar where the sequences between the animal and human strains, circulating in the same geographic region, are closely related with evidence for zoonotic infection. The geographical distribution of HEV genotypes is complex.

Genotype 1 consists of strains circulating in Africa and Asia (Egypt, Algeria, Morocco, Sudan, and Chad; India, Pakistan, Nepal, Bangladesh and China). Genotype 2 is found in Mexico and in some African countries (Nigeria, Namibia, Chad, and Sudan). Genotype 3 is widely distributed, mainly being reported in the USA, Europe and Japan. Genotype 4 is restricted to India and East Asia. However, genotype 1 viruses, and more recently genotype 4 viruses, are found in patients in Europe, North America and elsewhere after travelling to endemic areas and represent imported cases. Epidemics and sporadic cases of hepatitis E occur in areas of endemicity (genotypes 1, 2 and 4); more isolated clinical cases occur among a sizeable group of mostly asymptomatic seropositive residents in developed countries (genotype 3). There is increasing evidence of chronic infection with genotype 3 HEV in transplant patients with monitoring of viral loads in response to antiviral therapy. Initial studies in Japan revealed that HEV infection was widespread in blood donors (restricted to genotypes 3 and 4) and recent and on-going studies in China and Europe have demonstrated that HEV infection in blood/plasma donors also occurs with surprising frequency. From sequence analysis of different HEV strains, at the nucleotide level, there is in the order of 74% nucleotide identity between genotypes. In the case of genotype 3 for example, there are at least 10 sub-genotypes which vary by up to 15% nucleotide identity. In order to ensure appropriate coverage of NAT assays for HEV, the availability of a genotype panel would be a valuable tool.

At the annual meeting of the WHO ECBS in October 2011, the proposal was made by the PEI to develop an International Reference Panel for hepatitis E Virus genotypes. The ECBS endorsed the proposal. HEV-positive plasma donors have been identified and HEV strains available from these include 3c and 3f which are clinically important in chronic HEV infections in Europe. Additional stains available from earlier studies include 3b (Japanese derived), 3f (from Europe) with both seronegative and seropositive samples available, and 4c (from Japan). Gentoype 1 plasma samples have been obtained from India and are undergoing characterization. Further samples are being sought.

2.2.2 Development of an International Anti-HBe Standard
Hepatitis B virus (HBV) infection is a major health problem worldwide with an estimated 350 million chronic carriers. Approximately one third of the human population has been infected with HBV. The diagnosis of HBV requires a combination of various tests including detection of antibodies to HBe antigen (anti-HBe). The anti-HBe test is particular meaningful in association with the HBeAg test for monitoring the course of HBV infection. Anti-HBe without HBeAg can indicate the presence of precore stop codon mutants. Standardization of diagnostic test kits using an international standard for the detection of anti-HBe would provide a valuable tool for determination of analytical sensitivity of anti-HBe assays; calibration of secondary standards by kit manufacturers, control laboratories and end users. . Currently, no international anti-HBe standard is available. A proposal was presented in the WHO Collaborating Centers Meeting in March 2011 which was subsequently endorsed by the ECBS in October 2011. In 2011 and 2012, work focused on the identification and characterization of high titer anti-HBe material suitable to develop as a WHO International Standard. Finally, a plasma pool from three female Asian donors was prepared and batches of vials 2005, each containing 0.5 ml of plasma were lyophilized. . In addition, five further samples have been selected for inclusion in the collaborative study to demonstrate commutability of the candidate material.

Currently, 19 laboratories worldwide have agreed on to participate in the collaborative study including representatives from France, the Netherlands, Germany, the United Kingdom, the U.S.A., Canada, Brazil, Thailand, Korea, Japan, and Russia. The study materials will be distributed in July 2012 and it is expected that the report of the collaboratives study will be submitted to the WHO ECBS for review in 2013.

2.2.3 Development of an International HBeAg Standard
Hepatitis B virus (HBV) infection is a major health problem worldwide with an estimated 350 million chronic carriers. Approximately one third of the human population hasbeen infected with HBV. The Hepatitis e antigen (HBeAg) is a diagnostic marker for HBV infectivity. It is first detectable in the early phase of HBV infection, after the appearance of HBsAg. The titers of both antigens rise rapidly during

viral replication during the acute infection phase. Currently, no international HBeAg standard is available. Manufacturers have used the PEI HBeAg Reference Material 82 for the evaluation and development of improved HBeAg assays and for validation purposes. An international standard for HBeAg would be useful for determining analytical sensitivity and for quality control purposes by manufacturers and control laboratories as well as and for international standardization of HBeAg quantification in routine clinical diagnostics. A proposal was presented at the WHO Collaborating Centers Meeting in March 2011 and was subsequently endorsed by the ECBS in October 2011. A collaborative study was initiated in March 2012 with the aim to calibrate the candidate material in International Units (IU) and assess its suitability for use in a range of assays in different countries and laboratories. Participating countries include Europe (France, Netherlands, Germany, United Kingdom), U.S.A., Canada, Brazil, Thailand, Korea, Japan, and Russia. Three further HBeAg positive samples are also being evaluated in parallel to assess the commutability of the candidate standard.
It is expected that a report of the study will be submitted to the WHO ECBS for review in 2013.

2.3 Establishment of an International Standard for Mycoplasma NAT
PEI Project leaders: Micha Nübling, Thomas Montag-Lessing
In October 2010, the WHO Expert Committee on Biological Standardization (ECBS) had endorsed the project proposal to establish a WHO International Standard (WHO IS) for Mollicutes ("Mycoplasma") NAT. The Paul-Ehrlich-Institut was asked to conduct this project.
An international reference material for Mollicutes NAT is expected to be an important tool for the standardization of different nucleic acid tests designed for the detection of Mycoplasma contamination of biological materials and/or for diagnosis of Mycoplasma infections. NAT testing for Mycoplasma contamination plays an increasing role in the safety testing of biological materials used for the production of biological products, including biological medicines. Furthermore, regulatory authorities in different regions of the world increasingly accept Mycoplasma NAT testing as a replacement for (or in combination with) culture-based Mycoplasma detection methods. A WHO IS for Mycoplasma

NAT will be useful for:
•standardizing NAT assays of different design with a common material;
•performing validation of different methods with the use of a common material;
•reporting quantitative test results by different assays in a common unitage (International Units/ml), and expressing analytical parameters (e.g. limit of detection) in a common unitage.

Prior to the establishment of the candidate material, a feasibility study has now been started to evaluate different candidate materials, to determine the current consistency of result reporting by different assays and to investigate the suitability of a future WHO IS. A panel of lyophilized specimens containing different Mollicutes species (including e.g. Mycoplasma pneunomiae, Mycoplasma fermentans, Mycoplasma orale, and Acholeplasma laidlawii) were sent out to voluntary participants. Initial results of this study indicate the need for standardization of Mollicutes NAT and the interest in the field in a common calibrator material.

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

INNs are assigned to a range of biologicals including recombinant blood products, monoclonal antibodies and gene therapy medicinal products which fall under the responsibility of the PEI.

Dr Weisser assessed 65 INN requests of biological substances from July 2011 to June 2012. She attended two consultations of the INN expert group (53rd and 54th consultation in October 2011 and May 2012, respectively) where all comments were discussed and decisions on the selection of INNs were taken.

2.5 Cooperation with WHO in the area of WHO´s prequalification program for in vitro diagnostic devices (IVD) and procurement of IVDs
Between June 2011 and June 2012 the PEI IVD Laboratory participated in the WHO program for the prequalification of diagnostics (http://www.who.int/diagnostics_laboratory/evaluations/en/). Four HIV Rapid Test Devices (RTDs) were reviewed to assess the products and their performance: First Response HIV 1-2.O Card Test, Signal HIV Flow Through HIV 1+2 Spot/ Immunodot Test Kit, ImmunoComb II HIV 1&2 Trispot Ag-Ab, Reveal HIV Antibody Test. In addition, colleagues from the PEI IVD Laboratory participated in four on-site inspections to assess the effectiveness of the manufacturer's quality management system and the correct implementation of documented procedures of the reviewed RTDs: HIV 1/2 Stat-Pak (Chembio, New York, USA), Signal HIV Immunodot Test Kit Flow Through (Span Diagnostics Ltd., India), Reveal HIV Antibody Test (MedMira, Halifax, Canada), INSTI HIV 1/2 Antibody Test (bioLytical, Vancouver, Canada). The specialist support from the experts from the PEI IVD Laboratory enabled the WHO to procure high quality IVDs for high burden diseases.

In the context of a WHO field safety notice with an HIV Rapid Test Device (RTD) (http://www.who.int/diagnostics_laboratory/procurement/complaints/en/index.html), the lots already in the market of the concerned HIV RTD were quarantined by Global Fund. The PEI IVD Testing Laboratory was asked to test the quarantined lots. Twenty lots of the product were tested and reviewed for their conformity with specifications and absence of the concerned defect. The results helped WHO/Global Fund in the supply of quality-assured HIV RTDs.

In the context of the quality problems observed by the WHO with HIV RTDs, PSI (Population Services International, Washington, DC, USA) also contacted the PEI IVD Laboratory for testing of two HIV RTD lots, which PEI was able to confirm passed the specifications so that the supply with these products could be continued. PSI is a non-profit organization whose major donors include the governments of the United States, the United Kingdom, Germany and the Netherlands; the Global Fund to Fight AIDS, Tuberculosis and Malaria; United Nations agencies.

2.6. Training on Biotech Products Testing in the Centro Nacional de Control de Calidad" (CNCC), Lima, Peru, 29 October - 12 November 2011
Uwe Müller
The National Center for Quality Control, "Centro Nacional de Control de Calidad" (CNCC), part of the National Health Institute, "Instituto Nacional de Salud" (INS) requested "Training on Biotech Products". Together with the CNCC, a two week workshop ("Control de Calidad de Productos Biotechnologicos") was prepared, containing the following theoretical topics:
1.Overview of the Paul-Ehrlich-Institut (PEI) with its functions and duties in the regulation of medicines for the national and the European markets
2.The process of authorisation of medicines in Europe and Germany
3.The legislation of biotech products in Europe and Germany
4.The batch release system of the PEI with focus on biological medicines
5.Analytical methods established in PEI accredited for batch release (ISO 17025)
6.The quality management system of the PEI
7.Safety and efficacy of blood products

The workshop also contained practical sessions for tests established and used at the PEI; chromogenic -test and a clotting-test for Factor VIII containing products.

A group of 12 assessors of CNCC was trained in four groups in the above mentioned techniques.
In the morning the presentations were given in the lecture hall of the INS, followed by the theoretical background of the analysis methods and the lab-work in the afternoon. Standards, analytical reagents and test products were provided by PEI. CNCC contributed one older Factor VIII product, distributed by pharmacies in Peru. The aim of the practical part of the workshop was to estimate the activity of the product.
At the 5th Scientific Congress of the INS, a presentation of PEI and on legislation of biological medicines in Europe was given.

As a follow-up of the PEI - CNCC cooperation, a scientist of CNCC has applied for a grant from the

German Academic Exchange Service (DAAD), to spend one month in PEI, learning basic methods for the batch release of biological medicines. The decision of DAAD is scheduled for November 2012.

2.7 Meetings and Workshops at WHO HQ, Geneva

2.7.1 Stakeholder meeting to provide inputs on local production and access to medical products phase 2, Geneva 9 – 10 February 2012.
Phase 1 of this project identified the main challenges and obstacles to local production of medical products and technology transfer in developing countries. In phase 2 a common understanding of how to support local production and how to improve access to medical products was discussed. Opportunities for synergies were identified. PEI was represented by Dr Uwe Unkelbach.

2.7.2. Workshop on Improving access to safe blood products: a framework to improve public health, Geneva 14 – 15 June 2012
The workshop entitled "Improving access to safe blood products: a framework to improve public health" was chaired by Dr Harvey Klein, National Institutes of Health, USA. The objective of this meeting was to raise awareness of the significance of plasma-derived products as essential medicines and the need to improve the access of patients to safe blood products globally. Representatives, from all WHO regions, including participants from governments, regulatory authorities, blood donation services, the plasma industry, patient organizations, and NGOs such as the Bill Gates Foundation were present.

Rainer Seitz made a presentation about the World Health Assembly Resolution WHA63.12 on Availability, Safety and Quality of Blood Products. This Resolution expresses concern about the unequal access globally to blood products, particularly plasma-derived medicinal products, leaving many patients without adequate treatment, as well as concern that plasma from developing countries, because of insufficient regulatory controls and failure to implement appropriate practices in blood establishments, is often unacceptable for contract fractionation, with considerable wastage of plasma as a result. The presentation introduced the background and the messages of the Resolution.
There are already a number of important WHO guidance documents available, e.g. WHO Recommendations for the Production, Control and Regulation of Human Plasma for Fractionation. Recently, the WHO Blood Regulators Network (BRN) has drafted a document entitled "Assessment Criteria for National Blood Regulatory Systems". Nevertheless, the intention of the meeting was to emphasize that further, intensive and sustained efforts and financial resources will be needed in order to achieve the objectives of the Resolution WHA63.12.

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

2.8.1 IPFA/PEI (International Plasma Fractionation Association) 19th Workshop on Surveillance and Screening of Blood Borne Pathogens, Budapest, Hungary, 23 - 24 May 2012
PEI co-organizes this annual scientific meeting, the primary focus concerns the 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 one of the topics discussed regularly at the congress. Dr Micha Nübling, Dr Heiner Schleiblauer, Dr Julia Kress, Dr Sally Baylis and Dr Florian Neske participated in the workshop. This year's workshop had a special focus on new technologies such as next generation sequencing and their potential in identifying yet uncharacterized new pathogens. Dr Baylis gave presentation on virus clearance studies. These annual workshops attract more than 200 participants and are an ideal opportunity to update knowledge on blood safety and for informal discussions on related topics.

2.8.2 SoGAT: XXIII Scientific Working Group on the Standardization of Genome Amplification Techniques for the Safety Testing of Blood, Tissues and Organs for Blood-borne Pathogens. Vilnius (Lithuania), 16 – 17 April 2012
Dr Micha Nübling attended the meeting and gave several presentations on standardization projects performed by the PEI. Another presentation focused on the new developments in NAT screening in Europe (e.g. HEV in plasma pools for virus inactivated plasma) and on the new regulation expected for in vitro diagnostic devices.

2.9 Further conferences with CC relevant topics attended by PEI co-workers (chronological order):

XXIII congress of the International Society on Thrombosis and Haemostasis / 57th Annual SSC Meeting, Kyoto, Japan, 23 - 28 July 2011
PEI participants: Dr Anneliese Hilger and Dr Johannes Dodt. Dr Hilger gave a presentation on "Clinical trial requirements for FVIII/FIX - EU-regulatory perspective" in the SCIENTIFIC SUBCOMMITTEE SESSION on Factor VIII and IX.

14th Annual Meeting of the European Society for Clinical Virology. Funchal, Madeira, 21 - 24 September 2011. PEI participants: Dr Michael Chudy and Dr Sally Baylis. Dr Baylis presented a poster on "Laboratory performance for hepatitis E virus (HEV) RNA detection and development of a WHO International Standard".

PIC/S expert circle on human blood, tissues and cells. "Substances of Human Origin: the Good, the Bad and the Ugly", Tallinn, Estonia, on 26 - 30 Sept. 2011. PEI Participant and Moderator: Dr Uwe Unkelbach: Presentation: "Case Studies of Counterfeited Biological Products and Certificates"

14th Planova Workshop, 9 - 10 November 2011. PEI participants: Dr Johannes Blümel and Dr Sally Baylis. Dr Blümel made a presentation on "Experience with reduction of small non-enveloped viruses".

European Directorate for the Quality of Medicines & Health Care, EDQM in Strasbourg, 10 - 11 May 2012: "Batch Release For Medicinal Products Derived From Human Blood and Plasma: Principles, Procedures And Tools. PEI Participant and Moderator: Dr Uwe Unkelbach, presentation on "Control Authority Batch Release Beyond The EU"

PDA/FDA Virus and TSE safety Conference, Bethesda, MA, USA, 15 – 17 May 2012.
PEI participant: Dr Johannes Blümel, presentation on "Detection of HEV Genotypes in Human Blood".

Viral Safety for Biologics, Cologne, Germany, 27 - 28 June 2012. PEI participant: Dr Sally Baylis. Dr Baylis gave a presentation on "Hepatitis E virus – of swine and men".

3. Please briefly describe any interactions or collaborations with other WHO collaborating centres in the context of the implementation of the above activities (if any). If you are part of a network of WHO collaborating centres, please also mention the name of the network, and describe any involvement in the network during the last 12 months.

3.1 Participation in collaborative studies of WHO International Blood Product Standards

The Batch Release of Blood Products, Logistics section of PEI participated in several collaborative studies in 2011/2012. The proposed candidate WHO International Standard (IS) materials were processed at NIBSC, UK according to the WHO guidelines for the production of reference materials.
Based on a collaborative study which the PEI participated in, the WHO Expert Committee on Biological Standardization (ECBS) decided to establish the 3rd International Standard (IS) for Fibrinogen, Plasma WHO in 2011.
Collaborative StudyOrganized by
1st IS C1-Inhibitor, Concentrate (08/256)NIBSC, UK
1st IS C1-Inhibitor, Plasma (08/262)NIBSC, UK
The PEI's results were in good agreement with the other participating laboratories.
PEI was also involved in other collaborative studies conducted during the reporting period:
•Collaborative study for the value assignment of the 2nd IS for Fibrinogen, Concentrate. Some of the participants raised concerns about the first proposal to assign a value combined from the results obtained by different methods (Clauss vs. Clot removal), where a discrepancy of ~ 20% was observed. It was decided to carry out a Field Study which the PEI also participated in, to assess the actual potency discrepancy between methods. The recently revised proposal is to assign a value based only on clot removal assay results. The final decision for the value assignment is still pending.
•Collaborative study to calibrate the 2nd WHO IS for Factor VII concentrate. It is proposed that this standard should be established with two assigned values, one for chromogenic and the other for clotting assays due to significant differences between the potency estimates by the different methods. The final decision for the value assignment is still pending.
•Collaborative study for value assignment of the 4th WHO IS for Factors II & X, concentrate. The final decision for the value assignment is still pending.
PEI (sections "Batch Release of Blood Products, Logistics" as well as "Blood coagulation products II") also took part in international collaborative studies to establish secondary plasma standards:
•ISTH/SSC (International Society on Thrombosis & Haemostasis/ Scientific and Standardization Committee) Secondary Coagulation Plasma Standard Lot #4.
PEI carried out assays to calibrate the reference preparation for Protein C, Protein S, Factor XI, Factor V, Factor VIII Clotting Activity, Factor VIII Chromogenic Activity, vWF Ristocetin Cofactor Activity, vWF Collagen Binding Activity, vWF Antigen, Fibrinogen, and Factor XIII. The standard has been available since April 2012.
•Collaborative study (BSP 051) for the calibration of the European Pharmacopoeia BRP batch 1 and 2 for human coagulation factor V, VII, XI & XIII in normal human plasma.

3.2 Participation in collaborative studies for the replacement of WHO International Standards for NAT-based assays for blood borne viruses
The Molecular Virology section, part of the Virology Division at PEI, participated in three studies to replace WHO International standards for blood borne viruses which were established at the WHO ECBS meeting in October 2011 i.e. the 3rd HIV RNA IS, the 3rd HBV DNA IS, and the 4th HCV IS.
In addition the following standard will be submitted to ECBS in October 2012 for establishment.
Collaborative StudyOrganized by
Proposed IS2nd International Subtype Reference NIBSC, UK
Panel for HIV-1 NAT