Folder eCC_00005016 is in stage Annual_Report_Due

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	07-2012 to 07-2013		

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.

Sally Baylis
The 1st International Reference Panel (IRP) for B19V Genotypes was adopted by the Expert Committee on Biological Standardization (ECBS) in October 2009 (WHO/BS/09.2122).
The IRP is available from CBER/FDA and NIBSC (CBER Parvovirus B19 Genotype Panel 1, NIBSC code number 09/110, respectively).
Literature
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.

Sally Baylis
The 1st International Standard (IS) for HEV RNA was adopted by the Expert Committee on Biological Standardization (ECBS) in October 2011 (WHO/BS/09.2122).
The IS is available from PEI (PEI code number 6329/10).
Literature
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.
Baylis SA, Blümel J, Mizusawa S, Matsubayashi K, Sakata H, Okada Y, Nübling CM, Hanschmann KM; HEV Collaborative Study Group. World Health Organization International Standard to harmonize assays for detection of hepatitis E virus RNA. Emerg Infect Dis. 2013;19:729-35 (see also http://www.ncbi.nlm.nih.gov/pubmed?term=HEV%20Collaborative%20Study%20Group%5BCorporate%20Author%5D).

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.

Eva Spindler-Raffel, Thomas Montag-Lessing †
Bacterial contamination of platelet concentrates (PCs) still remains a persistent problem in transfusion [1]. To mitigate the risk of bacterial contamination of blood components, blood centres have implemented donor screening along with 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, e.g. in PCs during storage [2].
The International Society of Blood Transfusion (ISBT) Working Party Transfusion Transmitted Infectious Diseases (WP-TTID), Subgroup on Bacteria (former chair: Dr Thomas Montag-Lessing †) had organized an international study on Transfusion Relevant Bacteria References (TRBR) to be used as a tool for development, validation and comparison of the respective methods.
A four member panel was established, consisting of deep-frozen bacterial strains of four different bacterial species Staphylococcus epidermidis PEI-B-P-06, Streptococ-cus pyogenes PEI-B-P-20, Escherichia coli PEI-B-P-19, and Klebsiella pneumonia PEI-B-P-08. The panel members are bacterial strains selected for their ability to repli-cate in blood platelet concentrates (PCs) under routine storage conditions used in transfusion medicine. They are prepared using a specifically 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 and, potentially, technologies for pathogen reduction in PCs under "real life" conditions, i.e. inoculation the PCs with a very low bacteria count (0.03 to 0.3 CFU/ml) followed by growth in the matrix.
The panel of four bacterial strains was adopted by ECBS in 2010 as the 1st WHO International Reference Repository of Platelet Transfusion Relevant Bacterial Strains [3]. The strains are cultivated and distributed by the Paul-Ehrlich-Institut (PEI code number 8483/13). The committee requested detailed instructions for use, which were provided by PEI in February 2011.
The proposal for future expansion of the repository was also endorsed by ECBS in 2010
The potential bacterial candidate strains were discussed during several meetings of WP-TTID, Subgroup on Bacteria. At the end of the discussions, 11 candidate strains (as listed) were selected end of 2012 for the random study:
Aerobic spore forming bacteria: Bacillus cereus spores PEI-B-P-07-S, Bacillus thuringiensis spores PEI-B-P-57-S
Gramnegative species: Enterobacter cloacae PEI-B-P-43, Morganella morganii PEI-B-P-74, Proteus mirabilis PEI-B-P-55, Pseudomonas fluorescens PEI-B-P-77, Salmonella cholerae-suis PEI-B-P-78, Serratia marcescens PEI-B-P-56
Coagulase positive Staphylococcus: Staphylococcus aureus PEI-B-P-63
Streptococcus species: Streptococcus dysgalactiae PEI-B-P-71, Streptococcus bovis PEI-B-P-61

To characterize candidate strains for enlargement of the WHO Repository, which should be able to grow in PCs from very low initial concentrations, mimicking contamination with few bacteria, a random study was started 1st quarter of 2013 with test laboratories in different regions of the world. The deep frozen bacteria (the 4 strains of 1st WHO International Reference Repository of Platelet Transfusion Relevant Bacterial Strains plus 11 candidate strains) were shipped to the participating laboratories. At the request of ECBS, the Repository strains will be included again in the enlargement study as reference strains.
The study protocol includes enumeration of inoculum, low spiking of test bacteria directly in PC – bags (inoculum-concentration 10 to 25 cfu per PC bag). Growth kinetics will be documented by sampling and enumeration after storage day 2, 4 and 7.
New lots of the four WHO Repository strains (Staphylococcus epidermidis, PEI-B-P-06, Streptococcus pyogenes, PEI-B-P-20, Klebsiella pneumoniae PEI-B-P-08 and Escherichia coli PEI-B-P-19) were produced Stability testing and identification were completed in autumn 2012. Production processes, stability testing, and identification of 11 enlargement candidate strains were also completed end of 2012. The shipment of the 11 candidates as well as the 4 WHO Repository strains started (Q4, 2012, Q1 and Q2 2013). Start of the study (Q1, 2013) with 13 collaborating labs (Canada 1, USA 3, Mexico 1, England 1, The Netherlands 1, Germany 3, Austria 1, South Africa 1, and Japan 1).
Literature
1_Palavecino EL, Yomtovian RA, Jacobs MR. Bacterial contamination of platelets. Transfus Apher Sci. 2010; 42:71-82.
2_Montag T, Strategies of bacteria screening in cellular blood components. Clin Chem Lab Med. 2008; 46:926-32.
3_ Störmer M, Arroyo A, Brachert J, Carrero H, Devine D, Epstein JS, Gabriel C, Gelber C, Goodrich R, Hanschmann KM, Heath DG, Jacobs MR, Keil S, de Korte D, Lambrecht B, Lee CK, Marcelis J, Marschner S, McDonald C, McGuane S, McKee M, Müller TH, Muthivhi T, Pettersson A, Radziwon P, Ramirez-Arcos S, Reesink HW, Rojo J, Rood I, Schmidt M, Schneider CK, Seifried E, Sicker U, Wendel S, Wood EM, Yomtovian RA, Montag T. Establishment of the first international repository for trans-fusion-relevant bacteria reference strains: ISBT working party transfusion-transmitted infectious diseases (WP-TTID), subgroup on bacteria. Vox Sang. 2012; 102:22-31.

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.

Michael Chudy, Micha Nübling
The proposed 1st International Reference Panel for HBV genotypes (PEI code number 5086/08), intended for use with HBV NAT assays, 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.
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), consisting of 15 different members and representing HBV sub genotypes A1 (2), A2, B1, B2, C2 (3), D1, D2, D3, E, F2 (2), and H, has been described in the previous report.
The panel was adopted by ECBS as WHO International Reference Panel in 2011.
Literature
Peer-reviewed Publications on the projects are available:
Chudy, M., Hanschmann, K.-M., Kress, J., Nick, S., Campos, R., Wend, U., Gerlich, W., Nübling, C.M. (2012) 1st WHO International Reference Panel containing Hepati-tis B Virus Genotypes A - G for assays of the viral DNA. J Clin Virology 55, 303-309.
Chudy, M., Scheiblauer, H., Hanschmann, K.-M., Kress J., Nick, S., Wend, U., Schüttler, C., Nübling, C.M., Gerlich, W.H. (2013) Performance of hepatitis B surface antigen tests with the first WHO international hepatitis B virus genotype reference panel. J Clin Virology, http://dx.doi.org/10.1016/j.jcv.2013.06.011.

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.

Michael Chudy
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. 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 was undertaken in close cooperation with the Institute of Hepatology, Ankara University, Turkey. 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 was that EASL strongly support the standardization efforts.
The candidate standard is a lyophilized preparation of HDV genotype 1 strain, obtained from a clinical plasma specimen, diluted in negative human plasma. Fifteen laboratories from nine countries participated in a collaborative study to evaluate with their routine HDV NAT the candidate preparation (sample 1 and sample 2) alongside the corresponding liquid-frozen bulk material (sample 3) and a liquid frozen neat HDV RNA positive plasma specimen (sample 4). The results of the study indicate the suitability of the candidate material (sample1 and sample 2, HDV genotype 1) as the proposed 1st WHO standard for HDV RNA. It is therefore proposed that the candidate material (PEI code 7657/12) is established as the 1st WHO International Standard for HDV RNA for NAT-based assays with an assigned potency of 5.75×105 International Units per ml (IU/ml) when reconstituted in 0.5 ml of nuclease-free water. On-going real-time and accelerated stability studies of the proposed International Standard indicate that the preparation is stable and suitable for long-term use at the proposed storage conditions. The final report of the collaborative study was submitted to the ECBS in July 2013 for establishment of the 1st International Standard for HDV for NAT-based assays.

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.

Andreas Hunfeld, Johannes Dodt, Rainer Seitz
This project was put on hold when the working group met in February 2012 during the congress of the "Gesellschaft für Thrombose- und Hämostaseforschung" (GTH) in St. Gallen, Switzerland, since 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. This view was not changed when the group met again in June 2013 during the congress of the International Society on Thrombosis & Haemostasis (ISTH) in Amsterdam, Netherlands. Nevertheless, the PEI continues to be interested in establishing the 1st International Standard for factor XIII concentrate, and will take part in any new initiative aiming at establishing the 1st International Standard for factor XIII concentrate.

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.

Herbert König, Andreas Hunfeld, Johannes Dodt, Rainer Seitz
There are discrepancies between results of chromogenic and 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.
This phenomenon has even led to the authorization of certain products in the EU (ReFacto AF) and the rest of the world (XYNTHA) containing the same recombinant B-domain-deleted FVIII labelled with the same activity expressed in IU, but actually containing a significantly (factor 1.4) different amount of active substance due to the different assays used.
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 methodologies 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, Dr Dodt and Professor Seitz of PEI took part in the SSC (Scientific and Standardization Committee)/ISTH Factor VIII / Factor IX Sub-committee Project on the Potency of Clotting Factor Concentrates, which recently published a paper entitled "Recommendations on the potency labelling of factor VIII and factor IX concentrates" in Journal of Thrombosis and Haemostasis, 11: 988–989;2013.
In June 2013, during the ISTH congress in Amsterdam, Professor Seitz took part in a Global Haemostasis Tests meeting organized by the chair of the SSC/ISTH Factor VIII / Factor IX Sub-committee, where an expert panel including industry, academia and regulators explored the option of developing global tests such as thrombin generation assay for measuring FVIII in products. The prevailing view was that, for the time being, chromogenic and one-stage clotting potency assays remain the relevant potency tests, and the industry representatives strongly advocated further harmonization.
Intensive discussions about the FVIII assay issue in Expert Group 6B of the European Pharmacopoeia led to a proposal for a workshop on "Characterization of new clotting factor concentrates (FVIII, FIX) with respect to potency assays used for labelling and testing of post infusion samples" which will be organized by EMA and EDQM in November 2013. The workshop chaired by Dr Dodt is open to representatives of regulatory agencies, industry representatives, patient organizations and members of working groups of EMA (BWP and BPWP) and EDQM (Group 6B). The workshop will highlight potency determination issues of new clotting factor concentrates.

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.

Andreas Hunfeld
This activity was completed with assignment of the potency and adoption of the preparation during the ECBS meeting in October 2010. The concentrate 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

Gerd Werner
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.

Rainer Seitz, Margarethe Heiden
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.
The BRN reported to the ECBS during the regular ECBS meeting at WHO headquarters in Geneva and met for a closed meeting on 18 October 2013. Furthermore, BRN telephone conferences were held on 28 August, 25 September, 10 December 2012, and on 21 May 2013.
The BRN supported the Secretariat in preparing the ICDRA 2012 in Tallinn, Estonia by organizing a pre -ICDRA workshop on Blood and Blood Components as Essential Medicines, and an ICDRA workshop on blood cell therapies. In the latter workshop, Professor Cichutek, President of PEI contributed a presentation on blood cell therapies.
A major focus of the BRN in the past years was the finalization 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 Resolution on Availability, Safety and Quality of Blood Products (WHA 63.12). The final document was posted on the WHO BRN website subsequent to the BRN meeting in October 2012.
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).

Gabriele Unger
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 Trainee from the National Pharmaceutical Control Bureau (NPCB), Ministry of Health, Malaysia, 11–19 Oct. 2012
A colleague from the NPCP spent seven days at the institute to learn about blood products regulation and inspection of plasmapheresis centres.
The individual training programme included the following contents:
Inspection Services for Biological Medicinal Products
•Inspection of plasmapheresis centres on the national and international level
oInvolvement of the PEI in inspections concerning human plasma for fractionation:
?national inspections (issuance of manufacturing authorization and routine/surveillance inspections);
?inspections for the issuance of a German import authorization/certificate;
?inspections initiated by the European Medicines Agency (EMA) as part of the Plasma Master File certification procedure (PMF-Inspections).
oSite visit at a German plasmapheresis centre and testing laboratory with representatives of the national competent authority (Regierungspraesidium Darmstadt) and the Paul-Ehrlich-Institut;
oSite visit at a German fractionation plant and the respective testing laboratories with representatives of the national competent authority (Regierungspraesidium Darmstadt) and the Paul-Ehrlich-Institut;
oPlasma Inspections in the US – a virtual tour through a US plasma-pheresis centre;
oPlasma Inspections in the US – topics covered and differences ob-served between US and German plasmapheresis centres;
oInspection reports for plasmapheresis centres, testing laboratories and warehouses (EMA inspections as part of the Plasma Master File certification procedure);
oInvolvement of the section “Inspection Services for Biological Medicinal Products” in the PMF assessment.

•EU-guidelines relevant for inspections concerning human plasma for fractionation

oDirective 2002/98/EC - ”Blood Directive“ – ”Mother Directive“;
oDirective 2004/33/EC - Technical requirements for blood and blood components;
oDirective 2005/61/EC - Traceability requirements and notification of serious adverse reactions and events;
oDirective 2005/62/EC - Standards and specifications relating to a quality system for blood establishments;
oDirective 2003/94/EC - Principles and guidelines of GMP …;
oEuropean Pharmacopeia – Monograph 0853 "Human Plasma for Fractionation“;
oEU-GMP guide – Annex 11, 14 and 15;
oGuideline on the Scientific Data Requirements for a PMF (EMEA/CHMP/BWP/3794/03 Rev.1);
oGuideline on Plasma-Derived Medicinal Products (EMEA/CHMP/BWP/706271/2012).

Blood coagulation products (plasma derived and recombinant)
•Licencing of Blood Coagulation Products
oNational Procedure
oCentralized Procedure
oPlasma Master File
oMutual Recognition Procedure.

Quality of plasma derived and recombinant blood coagulation factors
•Plasma derived products
oPlasma Quality
•Recombinant products
oCAP testing
•Licensing procedures
oNational Procedure
oDecentralized Procedure
oMutual Recognition Procedure
oCentralized Procedure
•Relevant monographs and guidelines
oScientific Data Requirements for a Plasma Master File
oPlasma derived Medicinal Product Guideline
•Dossier evaluation
oDossier structure eCTD (EURS is Yours) and Guidance on Assessment of the Quality Part in general
oCase Study for von Willebrand Factor (Wilate 500 IU, 1000 IU) - Decentralized Licensing Procedure.

Batch release of coagulation factors, albumin and other blood products
•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
oFV-clotting test
oAntithrombin – chromogenic test
oPrekallikreinactivator – chromogenic test.

Transfusion Medicine
•Licensing of blood components for transfusion and of stem cell preparations for hematopoietic reconstitution
oNational procedure
?Dossier evaluation
?Quality
oVariations
oInspections (inspections initiated by PEI in connection with licensing and regular inspections initiated by regional competent authorities respectively)
•Reports on National blood and hematopoietic stem cell supply
•Relevant guidelines / laws / Pharm. Eur.

oRegulatory guidelines
?National guidelines on blood components and stem cells
?European guidelines on blood and blood components and on cells and tissues (Directives 2002/98/EC, 2004/33/EC, 2005/61/EC, 2005/62/EC, 2011/38/EC, 2004/23/EC)
oNational laws (drug law, transfusion act)
oPharm. Eur. (Human haematopoietic stem cells).

11.2 Guests from Korea Food and Drug Administration (KFDA, now Ministry of Food and Drug Safety, MFDS), Republic of Korea, 19–23 Nov. 2012
Three colleagues from the KFDA spent a week at PEI to gain insight into the institute`s system of regulation of source plasma and blood products, including monoclonal antibodies.
11.3 Trainees from the Reference Health Laboratory, Ministry of Health and Medical Education, Islamic Republic of Iran, 15–19 Apr. 2013
Two colleagues of the Iranian Reference Health Laboratory spent a week in the WHO Collaborating Centres unit PEI IVD Testing Laboratory (in vitro diagnostic devices).
The training comprised the following areas:
Virus testing / In vitro diagnostic (IVD) test kits
•Process of prequalification of IVD particularly high risk classes (including the challenges in technical file assessment, review of CTS and protocols of laboratory evaluation);
•Evaluation parameters mostly considered in the institute;
•Process of CE marking and value of laboratory testing (type examination), design certification;
•Quality Management System (QMS);
•Using results of proficiency testing in IVD evaluation;
•ISO and German national standards applicable in IVD environment;
•Visit of IVD NAT Manufacturer: GFE Blut mbH, Germany, Altenhöferallee 3, 60438 Frankfurt am Main, Germany, http://www.gfeblut.de;
•Procedures for carrying out Post Marketing Surveillance (PMS) programme: not applicable: PMS is mostly carried out by federal authorities (“Länderbehörden”);
•Inspecting IVD manufacturing site: has not been performed as inspections are in the responsibility of federal authorities (“Länderbehörden”).

With respect to the testing of nucleic acid amplification tests (NAT IVDs), the agenda comprised the following topics in detail:
•Regulations in Europe (NAT IVD, safety testing of biologicals)
•Standardization of NAT IVDs
•WHO Project for HBV- and HDV-NAT
•Batch verification of CE marked NAT IVDs, NAT laboratories
•Plasma Master File Regulation.

With respect to the testing of serological IVDs, the agenda comprised the following topics in detail:
•Process of WHO prequalification of IVDs
•Process of CE marking
•Hepatitis B Virus detection: HBsAg (sensitivity/specificity, mutant detection)
•Batch verification of CE marked serological assays
•Participation in Proficiency Testing
•WHO-Project anti-HBe Standard
•Challenges in the assessment of technical files
•Common Technical Specifications of the European Community for IVDs
•WHO-Project Hepatitis B: WHO International Standard for HBeAg
•WHO-Project WHO International Standard for Cytomegalovirus (CMV)
•Quality Management System.
Visit of the PEI-IVD laboratory.

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.

Rainer Seitz, Margarethe Heiden
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.

Sigrid Nick, Heiner Scheiblauer
A proposal to develop an International Hepatitis C Virus Core Antigen (Ag) standard was presented in the WHO Collaborating Centres Meeting in February 2009 and was subsequently endorsed by the ECBS in 2009. In 2011 and 2012 the project activities focussed on the search and characterization of a suitable high titre HCV core Ag material of genotype 1 available in sufficient quantities for use in both, HCV core Ag and HCV Ag/Ab (antigen/antibody) combination tests. Finally two HCV core antigen positive donations originating from one US blood donor collected in 1996 and drawn on two occasions two days apart could be obtained. In-depth characterization of the material showed that it was suitable for both highly sensitive HCV core Ag assays and HCV Ag/Ab combination assays with lower sensitivity for HCV core Ag. In the meantime, the material has been lyophilized, and 1847 ampoules à 0.5 ml have been produced. The lyophilized material has been demonstrated to maintain its reactivity in HCV core Ag and HCV Ag/Ab assays. Further three high titre materials were selected and characterized to evaluate commutability of the candidate standard. At the 4th Meeting of WHO Collaborating Centres in April 2013 (see below, 3.1) it was discussed that it would also be reasonable to include a fourth sample with low content of HCV core Ag reactive by HCV core Ag assays only. Next steps will be the initiation of a collaborative study to establish the 1st HCV core Ag International Standard by 2014 and to investigate the stability of the lyophilized material.

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 63rd ECBS Meeting, Geneva, Switzerland, 15-19 October 2012
The Paul-Ehrlich-Institut as WHO Collaborating Centre (CC) for Quality Assurance of Blood Products and in vitro Diagnostic Devices is 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. His presentation focused on biological measurement standards provided by the PEI as WHO Collaborating Centre. This list of standards will be extended by a HEV genotype reference panel which will include the major genotypes identified in humans. The bacteria repository will be expanded by new strains established in close cooperation with the International Society of Blood Transfusion (ISBT). For HDV RNA, the 1st WHO IS will be presented for adoption by ECBS in 2013. The same timeline is planned for the anti-HBe WHO IS and the HBeAg 1st WHO IS. Good progress has been made with the Mollicutes (Mycoplasma) NAT standardization project. Issues on the 1st WHO IS Factor XIII and on Factor VIII potency assays were mentioned. The discussion covered the commutability study planned for the WHO IS HEV RNA and potential outsourcing of standardization activities.
Dr Micha Nübling, rapporteur of the Blood Products Track of the ECBS meeting, also participated in the plenary session on the first day and in the blood track on the subsequent days.
The main topics at the 63rd ECBS included "Strategies to promote availability and safety of blood products", a project led by Dr Padilla (WHO) and Dr Burnouf (WHO), with contributions expected from the WHO CCs. A kick-off meeting at WHO HQ on this topic in June 2012 was attended by Professor Seitz and Dr Nübling. The aim of the project is to use the recovered plasma in low and middle income countries instead of discarding it. Indonesia will be one of the pilot countries for this project.

In this respect, the topic of "Residual risk in recovered plasma" is planned to be addressed by a guidance document. Major contributions are expected from R. Reddy (South Africa), M. Nübling (PEI) and A. Padilla (WHO).
Another major topic was "Blood and blood components as essential medicines". The potential inclusion of blood into the WHO list of essential medicines is expected to facilitate more appropriate support and infrastructure in blood systems in low and middle-income countries
The commutability of WHO Reference Preparations is a topic which was discussed several years ago and which came up again with more recent initiatives in the clinical chemistry community. The discussion at the ECBS resulted in the decision to organize a WHO workshop to address this important topic in respect to WHO reference materials provided in the infectious disease area. The workshop took place in the meantime (April 2013) and resulted in a better understanding of potential commutability aspects in relation to WHO International Standards and how they may be better addressed in the future. Collaborative studies may need to include clinical samples to exclude potential non-commutability. More detailed guidance for the WHO CCs needs to be established (see also below, 2.7.1).
The PEI project to draft a guideline on the preparation and calibration of secondary reference preparations in the IVD area was endorsed by ECBS. R. Seitz gave an update on the repository of transfusion relevant bacteria strains which have been established at the PEI. The current status of the Mycoplasma NAT project was reviewed by M. Nübling, with the expectation of final establishment of the WHO IS by the ECBS in 2013 (see also Activity 3 and point 2.2.1, respectively).

2.2 Progress Reports of projects endorsed at 61st ECBS Meeting, Geneva, Switzerland, 18-22 October 2010
2.2.1 Establishment of an International Standard for Mycoplasma NAT
Micha Nübling
In October 2010, the ECBS had endorsed the project proposal to establish a WHO International Standard (WHO IS) for Mollicutes (Mycoplasma) NAT. During the following years, a feasibility study with worldwide representation was performed which led to the identification of Mycoplasma fermentans as the most promising mycoplasma species for the use as the candidate WHO IS. In a comparability study, the candidate preparation was characterized and International Units proposed, close to NAT detectable units. The candidate WHO IS will be presented for adoption to the ECBS in October 2013.

2.3 Progress Reports of projects endorsed at 62nd ECBS Meeting, Geneva, Switzerland, 17-21 October 2011
2.3.1 Development of a Hepatitis E Virus Genotype Panel
Sally Baylis
The 1st WHO International Standard for hepatitis E virus is a genotype 3a strain; the virus was obtained from a 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 and 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 ongoing studies in China and Europe have demonstrated that HEV infection in blood/plasma donors also occurs with surprising frequency. From sequence analyses of different HEV strains, at the nucleotide level, there is nucleotide identity between genotypes in the order of 74%. 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. Since that time, HEV-positive plasma samples have been evaluated from blood/plasma donors including genotype 3c, 3e and 3f strains which are clinically important in chronic HEV infections in Europe. Additional strains available from earlier studies include 3b (Japanese derived), and 4c (from Japan) and these will be supplemented by a further genotype 4g sample from Japan. Genotype 1 plasma samples have been obtained from India and Africa which will be included in the panel. In addition, high titre stool samples are available and include a further genotype 1 virus strain from India and a sample from an immuno deficient French patient where the HEV strain is highly related to rabbit HEV. Procurement of genotype 2 HEV strains is currently under discussion.

2.3.2 Development of an International Anti-HBe Standard
Olivia Knauer, Heiner Scheiblauer
Standardization of diagnostic anti-HBe test kits using an international standard for the detection of anti-HBe provides a valuable tool for the determination of assay sensitivity. Currently, an international anti-HBe standard is not available. Such a standard material could serve for the determination of the analytical sensitivity of anti-HBe assays, for the calibration of secondary standards by manufacturers to adjust their test kits, for quality control by competent authorities and also by users. A proposal was presented at the 3rd WHO Collaborating Centres Meeting in 2011 which was subsequently endorsed by the ECBS. The activities in 2011 focussed on the characterization of high titre anti-HBe materials available in sufficient quantities suitable for use in anti-HBe tests. Finally a suitable high-titre material could be produced from three Asian blood donations. The material was filled in 2005 ampoules à 0.5 ml and lyophilized. Subsequently, a WHO collaborative study was carried out in 2012 to determine the potency of the candidate material compared to the current PEI anti-HBe standard. Twenty-one (21) laboratories from 12 different countries (France, The Netherlands, Germany, United Kingdom, US, Canada, Brazil, Thailand, Republic of Korea, Japan, Russia and China) participated in the study using 16 different anti-HBe assays. Additionally, three further anti-HBe samples originating from Africa were included in the collaborative study to demonstrate commutability with the standard candidate material.
Currently evaluation of the data of the collaborative study has been finished and a draft study report has been circulating among the contributing laboratories for comments. It is intended to propose the establishment of the 1st International anti-HBe Standard at the ECBS meeting in 2013.

2.3.3 Development of an International HBeAg Standard
Annette Reissinger, Sigrid Nick
The Hepatitis B 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 Hepatitis B surface antigen (HBsAg). The titres of both HBV antigens rise rapidly during viral replication in acute infection. Currently, an international HBeAg standard is not available. A proposal was presented at the 4th WHO Collaborating Centres Meeting in April 2013 (see also 3.1) and was subsequently endorsed by the ECBS in 2011. An international HBeAg reference preparation would be useful for the assessment of the sensitivity and the control of the quality of HBeAg test kits by manufacturers and regulators.
A WHO collaborative study was initiated in November 2012 to assess the suitability of a candidate material to serve as a standard for the detection of HBeAg in diagnostic assays. Two materials were compared: (1) the candidate HBeAg International Standard preparation (current Paul-Ehrlich-Institut (PEI) HBeAg standard, lyophilized) and (2) the current PEI HBeAg Standard (HBe-Referenzantigen 82). For the analysis of commutability of the candidate HBeAg standard, three additional HBeAg positive samples from Hepatitis B virus (HBV) infectious carriers were selected: (3) a high positive HBeAg serum sample (high positive for HBsAg), (4) a positive HBeAg serum sample (high positive for HBsAg), and (5) a low positive HBeAg plasma sample (high positive for HBsAg and for anti-HBe). Nineteen laboratories from 12 countries worldwide participated in the study and tested the materials using 14 different HBeAg assays. The dilution range of the candidate HBeAg material was within the dynamic measuring range of all assays. The endpoint titres ranged from 1:237 to 1:3904. As the PEI HBeAg standard (sample 2, 100 PEI U/ml) has been used worldwide since 1982, the antigen content of the candidate material was expressed relative to the PEI standard. The overall potency of the candidate material was 95 U/ml relative to the PEI standard. Samples 3 and 4 were detected positive by almost all assays, but signal levels differed substantially. Sample 5 was detected positive by nine

assays, but was missed by five assays. Those tests that failed to detect samples 4 and 5 as positive had the lowest endpoint titres using the candidate HBeAg material. This correlation was significant and thus supported commutability of the candidate material.
An accelerated stability study on the candidate HBeAg material revealed a stable recovery at temperatures up to 45°C for one week which may suggest long-term stability. A real time long-term stability study is still ongoing. Currently evaluation of the data of the collaborative study has been finished and a draft study report has been circulating among the contributing laboratories for comments. It is intended to propose the establishment of the 1st International HBeAg Standard at the ECBS meeting in 2013.

2.4 International Nonproprietary Names (INN) of blood products and monoclonal antibodies
Karin Weißer
Since May 2006, Dr Karin Weisser of PEI has been working as Biological Advisor for the International Nonproprietary Names (INN, i.e. generic names) expert group in line with the INN programme located at WHO headquarters. The programme is responsible for the selection and publication of INN for new pharmaceutical substances upon request by manufacturers. An INN identifies a pharmaceutical substance or active ingredient by a unique name that is globally recognized and is public property. The selection and publication of INNs fall under the responsibility of the WHO unit Quality Assurance and Safety of Medicines (QSM), Department of Essential Medicines and Health Products in the Health Systems and Innovation (HIS) cluster at WHO headquarters. 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.
In addition to the regular two consultations each year, separate WHO INN meetings on biological products have been held at intervals since 2002 to address general and specific aspects of nomenclature, including discussions on cell therapy products or biosimilars.
Dr Weisser assessed 56 INN requests of biological substances from July 2012 to June 2013. She attended two consultations of the INN expert group (55rd and 56th consultation in October 2012 and April 2013, respectively) where all comments were discussed and decisions on the selection of INNs were taken. In addition, she attended two separate discussion meetings on cell therapy products and on biosimilars on 15 October 2012 and 18 April 2013, respectively.

2.5 Cooperation with WHO in the area of WHO´s prequalification programme for in vitro diagnostic devices (IVD) and procurement of IVDs
Between June 2012 and June 2013, the PEI IVD Laboratory participated in the WHO programme for the prequalification of diagnostics (see http://www.who.int/diagnostics_laboratory/evaluations/en/). Activities in the context of the cooperation with WHO unit Diagnostics and Laboratory Technology, Department of Essential Medicines and Health Products in the Division Health Systems and Innovation (DLT/EMP/HIS), WHO HQ included the following:
1.Product dossier reviews for the Reveal HIV Antibody Test (Medmira), insti HIV-1/HIV-2 Rapid Antibody Test (bioLytical), Advanced Quality Rapid Anti-HCV Test (Intec), Premier Medical Corporation Ltd. First Response HIV 1-2.O Card Test, Span Diagnostics Ltd.Signal HIV Flow Through HIV 1+2 Spot/ Immunodot Test Kit, Orgenics/ Alere Ltd. ImmunoComb II HIV 1&2 Trispot Ag-Ab. These evaluations by PEI-IVD supported WHO in the preparation for the list of prequalified products on currently available HIV/AIDS, malaria and hepatitis B and C test kits and technologies.
2.Participation of Dr Heiner Scheiblauer as Temporary Adviser in a mission to Johannesburg/Pretoria, Republic of South Africa, from 18–23 August 2012 as in the official invitation letter: "The overall purpose of this mission is to obtain the necessary information from national institutions that will allow a fair assessment of the procedures for validation of HIV test kits and the subsequent technical tender process that leads to the selection of HIV test kits to be used in the public sector in the Republic of South Africa".
The specific objectives of the mission were the following:
•review laboratory procedures and methods used by the National Institute of Communicable Diseases (NICD) to evaluate SD Bioline HIV-1/2 3.0 and related diagnostics;
•review procurement procedures, specifically the technical tender process undertaken in the evaluation of SD Bioline HIV HIV-112 3.0;
•suggest methods and procedures to be used in future assessment/validation of HIV test kits for the purpose of tender process;
•advice on the establishment of a regulatory and procurement system with particular reference to

diagnostics;
•draft document for the procurement and evaluation of diagnostics.
3.WHO training workshop on post-market surveillance of HIV diagnostics at the Paul-Ehrlich-Institut, 21-23 February 2013. The meeting was organized by WHO/EMP/DLT and PEI-IVD. Participants included laboratory experts on HIV rapid testing from Côte d'Ivoire, Burkina Faso, South Africa, Tanzania, China, WHO/EMP/DLT, Institute of Tropical Medicine Antwerp Belgium and PEI-IVD. The aim of the meeting was to update the performance evaluations and lot testing activities for HIV rapid diagnostic tests (RDTs), to take stock of the current status with batch testing possibilities in the countries concerned, to review adequate methods for batch testing including requirements for internal quality control samples and to bring together and liaise participants for mutual exchange of the participant´s experiences. The outcome will be an executive summary report and a WHO batch testing protocol for HIV RDTs.
Further international activities in the broader context of the quality control of HIV Rapid test devices have been going on with Population Services International (PSI, Washington, DC, USA). PSI contacted PEI-IVD also in 2012 and 2013 for lot testing of various HIV RDT kits. In this context, PEI-IVD helps PSI to ensure continued supply of quality controlled HIV RDTs to developing countries. 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, as well as United Nations agencies.
In addition, three lots of an Anti-HIV-1/2 rapid test sampled in Armenia were tested by PEI-IVD on behalf of the Global Fund. The three lots were found acceptable and could be released for use.

2.6 Meetings and Workshops at WHO HQ, Geneva

2.6.1 WHO Consultation on Commutability of WHO Biological Reference Preparations for in vitro Detection of Infectious Markers, Geneva, Switzerland, 18-19 April 2013.
The consultation was attended by all stakeholders in the field of diagnostic assays (manufacturers, users, proficiency testing providers, academic community, WHO CCs). The presentations and discussions were separated for NAT assays and serological test systems. For PEI, Dr Nick, Dr Chudy, Dr Nübling, and Dr S. Baylis (via WebEx) participated in the consultation, with Dr Nick presenting issues with serological antigen assays and Dr Nübling introducing and summarizing the commutability of NAT assays. Further guidance – how to address commutability of future WHO ISs – will be defined by the WHO CCs as follow-up project of the consultation.

2.7 Other (non- WHO) meetings and workshops, related to WHO and PEI CC activities (chronological order)
2.7.1 IPFA/PEI (International Plasma Fractionation Association) 20th Workshop on Surveillance and Screening of Blood Borne Pathogens, Helsinki, Finland, 23-24 April 2013
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, with standardization of assays being one of the regular topics in this series of meetings. Dr Micha Nübling, Dr Michael Chudy, Dr Sally Baylis and the former president of PEI, Professor Johannes Löwer, attended this meeting. The 20th anniversary congress gave both a retrospective of achievements obtained in the field of blood safety and an outlook on expectations for the next ten years. Dr Nübling gave a presentation: "Assessment, Predictions and Speculations for the next 10 Years: Looking into the Future."
Further topics included potential new viral targets for blood screening, e.g. HEV, and the use of plasma in the developing world. The workshop attracted more than 250 participants, mainly from blood banks, academic institutions, regulatory authorities and diagnostic industry.

2.7.2 SoGAT (Standardization of Gene Amplification Techniques) – Joint 24th Blood Virology and 4th Clinical Diagnostics Meeting, Ljubiljana (Slovenia), 8-9 May 2013
In the first joint meeting of the two SoGAT groups (blood virology, clinical diagnostics), more recent developments in the field of diagnostic standardization were reviewed and new projects proposed and discussed. Dr Michael Chudy (PEI) gave an update on the WHO IS project for HDV RNA assays. Dr Micha Nübling (PEI) gave two presentations: "Update on the development of the 1st WHO International Standard for Mycoplasma" and "Update on recast of IVD Directive".
Discussions initiated by presentations of the PEI participants covered issues with standardization of HAV NAT and the need for a guideline on establishment of secondary standards. The important guideline project (initiated by WHO) will be followed up at the next SoGAT meeting in 2014 (Graz,

Austria) with a sufficient slot in the agenda for broad discussion.

2.8 Further conferences with CC relevant topics attended by PEI co-workers (chronological order):
32nd International Congress of the ISBT (International Society of Blood Transfusion) in joint cooperation with the 10th Congress of AMMTAC, Cancun, Mexico, 7–12 July 2012
WP-TTID Subgroup on Bacteria: Dr Eva Spindler-Raffel gave a presentation on the experimental preparatory work for the "Enlargement of WHO Repository PC Transfusion Relevant Bacteria Reference Strains".

USA Food and Drug Administration Center for Biologics Evaluation and Research (FDA/CBER) – Blood Products Advisory Committee Meeting, 20–21 September 2012
Hepatitis E Virus and Blood Transfusion Safety: Dr Sally Baylis gave a presentation about HEV NAT standardization.

European School of Transfusion Medicine (ESTM) Course "Appropriate use of plasma products". Zagreb, Croatia, 14–18 Nov. 2012
Dr Nübling gave a presentation: "Impact of epidemiology and screening strategies on plasma quality".

21st Annual Congress of the European Association of Tissue Banks (EATB). Vienna, Austria, 21–23 Nov. 2012
Dr Nübling gave a presentation: "Is it time to make NAT testing in tissue and cell donors mandatory?"

Rapid Microbiological Methods Conference. Munich, Germany, 11–12 Dec. 2012
Dr Nübling gave a presentation: "Update on WHO project for Mollicutes NAT standardization".

EUROPEAN SYMPOSIUM Optimal use of clotting factors and immunoglobulins, Wildbad Kreuth, Germany, 26–27 April 2013. The conference was organized by the European Directorate for the Quality of Medicines (EDQM) and co-sponsored by the Ludwig-Maximilians-University Munich and the PEI. The symposium was the third in a series, this time the main topics were novel coagulation factor products and immunoglobulins. Active participants (session chair, speakers, and rapporteurs of sessions) from PEI were Dr Hilger, Dr Kerr and Professor Seitz.

Plasma Product Biotechnology meeting 2013, Lanzarote, Spain, 13-17 May 2013
Dr Sally Baylis gave a presentation on hepatitis E virus.

23rd Regional Congress of the ISBT (International Society of Blood Transfusion), Amsterdam, the Netherlands, 2–5 June 2013
WP-TTID Subgroup on Bacteria: Dr Eva Spindler-Raffel gave a presentation on the Enlargement of WHO Repository Platelet Transfusion Relevant Bacteria Reference Strains.

2013 PDA Virus & TSE Safety Forum, Berlin, Germany, 3-6 June 2013
PEI participants: Dr Johannes Blümel and Dr Sally Baylis. Dr Blümel gave an update on European regulatory issues concerning adventitious agents with special emphasis on porcine-derived trypsin and development of a guideline. Dr Baylis gave a presentation on parvoviruses and plasma derivatives.

European Directorate for the Quality of Medicines & Health Care (EDQM), Annual Meeting of the OMCL Network, Helsinki, Finland, 13 June 2013
Dr Unkelbach reported on "Self-Reliance and Self-Sufficiency of Blood and Blood Products - the Iran Experience".

XXIV Congress of the International Society on Thrombosis and Haemostasis (ISTH), Amsterdam, the Netherlands, 29 June – 4 July
The congress was attended by Dr Hilger, Dr Etscheid, and Professor Seitz. Dr Hilger gave a presentation in the SSC Subcommittee on Factor VIII and IX and Rare Co-agulation Disorders on the topic: "New European pharmacovigilance legislation: First experiences". Professor Seitz participated in a Global Haemostasis Tests meeting organized by the chair of the SSC/ISTH Factor VIII / Factor IX Sub-committee, as mentioned in Activity 7. Dr Etscheid presented a poster and was co-author of an oral communication.

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 4th Meeting of WHO Collaborating Centres to support the development of WHO Biological Reference Preparations for blood products and in vitro diagnostic devices (IVD), WHO headquarters, Geneva, Switzerland, 16-17 Apr. 2013
The fourth meeting of the WHO Collaborating Centres was hosted by the Blood Products and related Biologicals; Quality Assurance and Safety: Medicines (QSM) Team, Department of Essential Medicines and Health Products (EMP), Cluster Health Systems and Innovation (HIS) at WHO headquarters.
The three WHO Collaborating Centres for biological standardization (WHO CCs), i.e. the National Institute of Biological Standards and Control (NIBSC, UK), the Center for Biologics Evaluation and Research, Food and Drug Administration (CBER/FDA, USA), and the Paul-Ehrlich-Institut (PEI) again focussed on biological reference preparations (BRPs) for IVDs with global importance for blood and blood products safety.
Participants of PEI included Dr Sally Baylis (via WebEx), Dr Michael Chudy, Dr Sigrid Nick, Dr Micha Nübling, Professor Rainer Seitz (via WebEx), and Dr Eva Spindler-Raffel (via WebEx).
Michael Chudy gave an update on the development of the 1st WHO IS for HDV for NAT-based assays. The report of the collaborative study was submitted to the ECBS in July 2013 for establishment (see above, Activity 5). Two further presentations by Michael Chudy covered issues with standardization of HAV NAT and the need for a guideline on establishment and calibration of secondary standards. A presentation by Micha Nübling covered the status of the project for the 1st International standard for Mycoplasma DNA (see also point 2.2.1).
Eva Spindler-Raffel gave an update on the progress of the expansion of the 1st WHO Repository of Platelet Transfusion Relevant Bacterial Reference Panel. The international enlargement study started in the first quarter 2013. Eleven bacterial strains were chosen which were agreed on during the meetings of ISBT WP-TTID Subgroup on Bacteria. Also included in the study were the four ECBS adopted repository strains. All strains were shipped to the participating laboratories to evaluate their ability to proliferate in platelet concentrates in different regions of the world (see also Activity 3).
Sigrid Nick informed the participants about the progress of the projects to develop the 1st International Standard (IS) for Anti-HBe antibodies; the 1st IS for Hepatitis Be antigen and the 1st International Standard for Hepatitis C Virus Core Antigen (see also 2.3.2, 2.3.3 and Activity 13).
A summary report of the meeting will be presented to the ECBS in October 2013.

3.2 Participation in collaborative studies of WHO International Blood Product Standards
The Batch Release of Blood Products, Logistics section of PEI, Division Haematology participated in several collaborative studies in 2012/2013. 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 in October 2012:
•the 2nd International Standard (IS) for Blood Coagulation Factor VII Concen-trate (10/252);
•the 4th IS for Factors II and X Concentrate (11/126);
•the 2nd IS for Fibrinogen Concentrate (09/242).
The PEI's results were in good agreement with the other participating laboratories.
PEI was also involved in an extensive Collaborative Study to investigate the comparability of recombinant and new generation Factor IX products with WHO IS for FIX Concentrate (CS503); the report of the study is pending.
Furthermore, PEI agreed to participate in Collaborative Studies to:
•establish a replacement batch for the Ph. Eur. BRP for Factor VIII Concentrate (BSP125);
•investigate potency discrepancies when assaying factor VIII Concentrates using different chromogenic test kits (BSP112).

3.3 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 several WHO collaborative studies in the reporting period:
•proposed 1st WHO International Reference Panel for HIV-1 Circulating Recombinant Forms for NAT Assays (NIBSC, UK);
•proposed 3rd WHO International Standard for Parvovirus B19 for NAT Based Assays (NIBSC, UK);
•proposed 2nd WHO International Standard for Hepatitis A Virus for NAT Based Assays (NIBSC, UK).