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Institution Name	Paul-Ehrlich-Institute (PEI)		
Name of the relevant department, unit, section or area of the institution			
Division of Haematology and Transfusion Medicine			
City	Langen		
Country	GERMANY	Reference Number	DEU-117
Title	WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices		
Report Year	07/2009 to 07/2010		

1. Implementation of the work plan. For each main activity briefly explain how the activity was implemented, the outcome and impact and, if available, the results of the evaluation (e.g. evaluation of a course by the participants). Also explain difficulties (if any). Do not provide technical results in this form (technical results, if applicable, are to be sent directly to the WHO Department you work with).

Activity 1 Development of International Reference Panel for Parvovirus B19 Genotypes for Nucleic Acid Amplification Technique (NAT)-Based assays

Explanation

Since 2004, European regulatory requirements have stipulated that plasma used in the production of anti-D immunoglobulin and pooled human plasma treated for virus inactivation must be screened to ensure that levels of parvovirus B19 (B19V) DNA do not exceed 10 IU/µl. The US Food and Drug Administration (FDA)/Center for Biologics Evaluation and Research (CBER) is currently recommending the screening of all plasma pools for B19V DNA. Variants of B19V have been identified in the last 10 years and these have been broadly divided into three genotypes. These variant viruses have been defined as species of B19V by the International Committee for the Taxonomy of Viruses, and both EDQM and CBER/FDA require that assays detect the different genotypes.
Between November 2008 and February 2009, a collaborative study to evaluate a panel of plasma samples containing different genotypes of parvovirus B19 (B19V) for use in nucleic acid amplification technique-(NAT)-based assays was undertaken. The study was coordinated between PEI, the Center for Biologics Evaluation and Research, Food and Drug Administration (CBER/FDA, USA and the National Institute of Biological Standards and Control (NIBSC, UK). The panels were prepared in the USA and comprise four different samples, i.e., Member 1, Member 2, Member 3 and Member 4 (M1-M4); these represent genotypes 1, 2, 3a B19V and a negative plasma control, respectively. Each laboratory assayed the panel members concurrently with the 2nd WHO International Standard (IS) for B19V DNA (NIBSC code 99/802) on 4 separate occasions and the data were collated and analysed at NIBSC. Thirty five laboratories from 13 different countries participated in the study. A total of 44 sets of data were returned; 34 from quantitative assays and 10 from qualitative assays. The majority of assays used were in-house and based on real-time PCR (polymerase chain reaction). The results showed that all 3 genotypes were detected consistently by the majority of participants, although a very small number of assays detected genotypes 2 and 3 less efficiently or not at all. Real-time stability studies have indicated that the panel of B19V samples is very stable under normal conditions of storage, i.e., at -70 ºC or below. The report of the study was submitted to the WHO ECBS in July 2009. The proposal to establish the panel as 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 panels are available from CBER/FDA and NIBSC (CBER Parvovirus B19 Genotype Panel 1, NIBSC code number 09/110).

Activity 2 Development of an International Standard for Hepatitis E Virus RNA for Nucleic Acid Amplification Technique (NAT)-based assays

Explanation

Hepatitis E virus (HEV) is a major public health concern, responsible for >50% of acute viral hepatitis cases in endemic areas (Africa, Asia, Central America) where sanitation is poor. 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 HEV are under development. Clinical laboratories, particularly hepatitis reference laboratories, as well as blood banks, plasma fractionation organizations and associated control laboratories may use the IS for the calibration of secondary standards.
An initial study has been 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. Although there were only a limited number of quantitative data sets, for the samples in the range of approximately 6-4 log10 copies/ml, the standard deviations of the geometric means of the samples ranged between 0.38 and 1.09. Except for one equivocal result, HEV RNA was not detected in the negative plasma controls. In general the assays used by participants were of reasonably good sensitivity. There were some notable exceptions where assays targeting HEV ORF1 resulted in reduced sensitivity or a complete failure of detection of HEV RNA highlighting the need for standardization of such assays. Only a single laboratory reported an equivocal false positive result for one of the negative samples. No single HEV strain of either genotype was consistently detected or quantified more readily than any of the others, and it has been proposed to develop either the genotype 3a or the genotype 3b strain into a candidate International Standard. The candidate standards will be lyophilized in August 2010 and the collaborative study will be run in conjunction with the Japanese National Institute for Infectious Diseases (NIID) who are developing a national standard in parallel.

Activity 3 Transfusion-Relevant Bacterial Strain Panel

Explanation

Bacterial contamination of platelet concentrates (PCs) remains a persistent problem in transfusion. No international transfusion-relevant bacterial strain panel currently exists for the investigation of methods used to detect or kill bacteria in blood components. Therefore the International Society of Blood Transfusion (ISBT) Working Party Transfusion-Transmitted Infectious Diseases (WP-TTID, Subgroup Bacteria), organized an international study on bacterial standards to be used as a tool for development, validation and comparison of both bacterial screening and pathogen reduction methods. Four blinded bacterial standards (A: Staphylococcus epidermidis; B: Streptococcus pyogenes; C: Klebsiella pneumoniae; D: Escherichia coli) were prepared and distributed to 14 laboratories in 10 countries. The panel members were well characterized (identity, cell density) and deep-frozen. The participating laboratories were asked to identify the bacterial species, estimate the bacterial count and determine their ability to grow in PCs after spiking at low levels (0.3 and 0.03 CFU/ml), to simulate contamination occurring during blood donation. Thirteen laboratories returned data concerning bacterial counts and identity; twelve laboratories returned data on the growth ability of the strains. The bacterial standards were correctly identified in 98% of cases (1 case reported as Staphylococcus delphini instead of the closely related S. epidermidis). S. pyogenes and E. coli could be grown PCs in 11 out of 12 laboratories (92.3%); in the case of K. pneumoniae and S. epidermidis these strains were grown by all participating laboratories. The results of bacterial counting were very consistent between laboratories: the 95% confidence intervals were for S. epidermidis: 1.19-1.32 x 107 CFU/ml, S. pyogenes: 0.58-0.69 x 107 CFU/ml, K. pneumoniae: 18.71-20.26 x 107 CFU/ml and E. coli: 1.78-2.10 x 107 CFU/ml. This international study demonstrated the stability of the bacterial standards and consistency of results in a large number of transfusion laboratories. The bacterial standards can be considered as a suitable tool in validation and assessment of methods for improvement of bacterial safety of blood components. The study is a first step in establishing an international reference panel for transfusion-relevant bacterial strains and will be enlarged in the near future.

Activity 4 Development of hepatitis B virus (HBV) genotype reference preparations for HBV DNA assays and HBsAg tests.

Explanation

The proposed HBV DNA genotype panel (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 found worldwide: Samples 1-3 (genotype A), Samples 4-6 (genotype B), Samples 7-9 (genotype C), Samples 10-12 (genotype D), Sample 13 (genotype E), Sample 14 (genotype F), and Sample 15 (genotype G). In the beginning of 2009 an international collaborative study was conducted to evaluate the panel for the use in NAT-based assays. Each laboratory analyzed the panel samples in parallel to the 2nd WHO International Standard (IS) for HBV DNA (NIBSC code 97/750) representing HBV genotype A2. Seventeen laboratories from 12 countries participated in the study. A total of 19 sets of data were returned; 16 from quantitative and two from qualitative NAT assays. One laboratory performed sequence and genotype analyses. The majority of NAT assays used were commercially available and based on real-time polymerase chain reaction (PCR). The results showed that the genotypes A–G were detected consistently by the majority of assays, although a small number of tests detected genotypes F and G less efficiently or not at all. Only a few genotype B, C, and E samples were under quantified by two methods. The finding that some NAT assays showed reduced detection efficiency with some of the non-A2 genotypes demonstrates the necessity of a well characterized genotype panel in addition to the WHO IS. Residual moisture content was determined to be 0.82% in the final container. Preliminary results of the real-time stability support the suitability of the panel for long term use. No unitage has been assigned to individual panel members. The final study report was submitted to the ECBS for consideration at the meeting in October 2009. The Committee established these materials as the 1st International Reference Panel for HBV Genotypes for NAT- Based Assays. The reference panel is held at PEI and is available on request. Information concerning the panel is available on the PEI website together with ordering details.

Activity 5 Establishment of the 1st International Standard for Hepatitis D Virus RNA

Explanation

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 WHO ECBS endorsed the proposal 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. 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. HDV RNA-high titre plasma samples (HDV-1) with a sufficient volume, provided by the Institute of Hepatology of the Ankara University, will be characterized in a feasibility study to determine suitable candidates for the preparation of the standard. The studies will include different NAT systems, as well the parallel testing with a well characterized armoured HDV RNA sample. The feasibility study will be performed by laboratories with expertise in molecular diagnosis of HDV. The potential candidate materials have a vial load from 105 – 107 copies/ml. The proposed standard preparation will consist of 2000 – 4000 vials containing approximately 105 copies HDV-RNA/vial. The fill volume will be between 0.5 – 1 ml per vial. A pilot study will be performed to ensure that the lyophilization process has no major influence on the integrity of HDV RNA. The worldwide collaborative study will be conducted to evaluate the candidate reference materials. The final report is expected to be submitted to the ECBS of WHO in July 2012 for establishment of the first International Standard for HDV RNA.

Activity 6 Preparatory work with the aim to establish the 1st International Standard for factor XIII concentrate

Explanation

The 1st IS for Factor XIII in Plasma was successfully established in 2006, however the development of a 1st IS for Factor XIII concentrate is being hampered by a number of issues, particularly the different matrix in concentrates compared to plasma. Further work is needed to overcome these issues. The Factor XIII Standardization Working Party under the auspices of the ISTH SSC subcommittee on Fibrinogen and Factor XIII is currently organizing the necessary collaborative work. The PEI is a member of the Working Party and participates actively in the ISTH SSC subcommittee on Fibrinogen and Factor XIII. Meanwhile, work is ongoing to optimize Factor XIII activity assays, including an assay developed in collaboration with the PEI (Oertel K., Hunfeld A., Specker E., Reiff C., Seitz R., Pasternack R., Dodt J. (2007) Analytical Biochemistry 367(2):152-158).

Activity 7 Exploration of a new factor VIII potency assay

Explanation

A major problem in the control of therapeutic Factor VIII (FVIII) products are the discrepancies found in potency values using different assays. This problem was discussed during the WHO Collaborating Centres meeting held at PEI in February 2009 supporting the development of WHO Biological Reference Preparations for Blood Products and in vitro Diagnostics. Discrepancies between the chromogenic and one-stage assays appear most pronounced in the immuno purified FVIII and the B-domain deleted product. It is not clear which assay best reflects clinical efficacy. Short term it would be preferable to use a product-based reference material, the activity of which is determined relative to the international reference unit. A new and improved assay reflecting clinical effectiveness is desirable. Thrombin generation is a possibility and PEI is working on a modified fluorogenic assay using FIXa as trigger and FXa as read-out, as presented at the 2009 GTH Annual Congress in Vienna (Gesellschaft für Thrombose- und Hämostaseforschung e.V./ Society of Thrombosis and Haemostasis Research). Currently, the method is being evaluated in collaboration with the University of Frankfurt using a variety of concentrates and clinical samples.

Activity 8 Participation in collaborative studies to establish the 2nd International Standard (IS) for von Willebrand factor (VWF) concentrate.

Explanation

PEI recently participated in the collaborative study to establish the 2nd International Standard (IS) for von Willebrand factor (VWF) concentrate (1st IS was established in 2001; WHO/BS/01.1947). The project has been coordinated by NIBSC, UK. The main aim in the recent study was to assign potencies for both ristocetin cofactor assay and collagen binding assay in a single standard preparation. The final decision for the assignment of the potency will be made during the next ECBS meeting in October 2010.
The rationale for the use of this standard has been described in the 52nd report of the ECBS (WHO Technical Report Series No. 924): “Von Willebrand disease is a haemorrhagic disorder caused by a deficiency and/or abnormality of plasma von Willebrand Factor (vWF). Purified concentrates containing vWF used in replacement therapy for von Willebrand disease must carry labels that state the concentration of vWF. Characterization of the vWF in therapeutic concentrates has been based on measurement of antigen (vWF: Ag), ristocetin cofactor activity (vWF : RCO), multimer composition and more recently collagen binding activity (vWF : CB). The vWF in therapeutic concentrates has been found to have a lower ratio of function/antigen than vWF in normal plasma and to lack the highest-molecular-weight multimers, probably as a result of degradation during purification. These properties, together with the obvious differences in purity between concentrates and plasma suggest that the currently available primary standard for vWF (the fourth International Standard for Factor VIII and von Willebrand Factor, Plasma, Human, coded 97/ 586), may not be the most appropriate reference material for the quantitation of vWF in concentrates.”

Activity 9 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”

Explanation

From the 13th of October 2008 until the 23rd of October 2009, Dr Gerd Werner was seconded to the Blood Products and Related Biologicals (QSD) Team (supervisor: Ana Padilla) within the unit of Quality Assurance and Safety of Medicines (QSM), Department for Essential Medicines and Pharmaceutical Policies (EMP), in the Health Systems and Services (HSS) cluster.
The scope of the secondment included activities relating to the establishment of a WHO Guideline on Good Manufacturing Practice (GMP) for Blood Establishments (see also Activity 12), as well as in the regulation of blood and blood products safety. The main activities were as follows:

- Preparation of a draft WHO guidance document on GMP for the production of blood components, including plasma for fractionation. The goal for the ECBS meeting in 2009 was to obtain approval for distribution of the draft document for official consultation. The ECBS approved the draft document for distribution for consultation in October 2009;
- Attendance at the ECBS meeting at WHO headquarters, Geneva, Switzerland in October 2009;
- Establishing an international network of collaborative organizations (regulatory agencies, blood establishments and other groups) interested in GMP;
- Organization of regional/global workshops on GMP for blood establishments (including regulatory agencies and fractionators) in support of the development of the guideline;
- Updating the web site on GMP with the material mentioned above: http://www.who.int/bloodproducts.

Since the completion of the secondment, Dr. Werner has been involved in the following activities concerning the WHO Guideline on GMP for Blood Establishments:

- Preparation of the draft document for consultation - January 2010:
- Evaluation of the comments after consultation (consultation from January to May 2010);
- Preparation of the final draft document for submission to the ECBS in August 2010.

The aim at the ECBS meeting in 2010 is to obtain the approval of the Guideline.

Activity 10 Participation in the Blood Regulators Network (BRN)

Explanation

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 2009, the BRN convened during the ECBS meeting on the 22nd of October at WHO HQ in Geneva. In addition, teleconferences are organized as required; in 2010, BRN telephone conferences took place on the 5th of March, and the 6th of May.
Currently the BRN comprises six 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 Members are (in alphabetical order of country): Therapeutic Goods Administration (TGA), Australia; Health Canada, Canada; Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), France; Paul-Ehrlich -Institut (PEI), Germany; Food and Drug Administration (FDA), USA, and Swissmedic, Switzerland. Each authority is represented by a member and an alternative member. The PEI representatives are Professor Rainer Seitz, who served for two years (2006 to 2008) as the first BRN chairperson, and Dr Margarethe Heiden. During the face-to-face meeting on 22 October 2009, a representative of Ministry of Health of Japan participated as a guest. He explained the Japanese interest in participating in the BRN. The current BRN Terms of Reference do not allow inclusion of new Members. The BRN will consider the information provided by the Japanese authorities and since other WHO member states may be interested in joining the BRN, it was decided to prepare a draft amendment of the Terms of

Reference for consideration of the ECBS and WHO Secretariat.
An important project of the BRN is the elaboration of Assessment Criteria for Evaluation of Blood Regulatory Systems. This project was 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. Initial impressions were presented at the BRN meeting on 22 October 2009; as soon as a detailed evaluation of the self-assessment exercise is available, the BRN will consider whether similar exercises for additional BRN members would be helpful, and discuss the further strategy to develop the Assessment Criteria for Evaluation of Blood Regulatory Systems.
Further topics discussed by the BRN in the reporting period included Member policies pertaining to preparedness of blood systems in the face of the influenza pandemic. Moreover, the BRN contributes to the programme of the ICDRA (WHO International Conference on Drug Regulatory Authorities) by presentations from BRN Members and organization of workshops. After the successful participation in the ICDRA 2008 in Bern, Switzerland, the BRN plans to contribute to the upcoming ICDRA 2010 in Singapore.
The BRN provided scientific input and support for a WHA resolution on the availability, safety, and quality of blood products. Through an initiative of the German Ministry of Health, the proposal for this resolution was brought forward by the European Union member states and Serbia to the WHO Executive Board. The PEI representatives provided information to the BRN about the progress of discussions, and advice to the German Ministry and the EU representatives, in developing the document. Finally, the resolution WHA63.12 was adopted by the 63rd World Health Assembly; the text is available on the WHO website: http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R12-en.pdf.
WHO/HSS/EMP/QSM/QSD* provides secretarial support for the activities of the network and acts as a central repository for information and documentation. The WHO provides the BRN members with a restricted web tool which facilitates exchange of messages and documents. The actual items of discussion, and the minutes of BRN meetings and teleconferences are confidential. However, general information about the BRN is available on the WHO website, and documents produced by the BRN for publication are posted at the following site: http://www.who.int/bloodproducts/brn/en/.
The BRN Position Paper on Collection and Use of Convalescent Plasma or Serum as an Element in Pandemic Influenza Planning was posted in July 2009.
*WHO Cluster Health Systems and Services/ Department of Essential Medicines and Pharmaceutical Policies / Unit Quality Assurance and Safety of Medicines / Quality Assurance and Safety: Blood Products and Related Biologicals Team.

Activity 11 Offer of Training courses for assessors working in regulatory authorities

Explanation

The training courses support the objectives of the WHO and the WHO Expert Committee on Biological Standardization (ECBS) to improve the regulation/control of blood products. This is also in line with the WHA Resolution 58.13 / Report EB113/10 and the new WHA resolution on availability, safety and quality of blood products (WHA Resolution 63.12).
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 help towards training costs.

11.1 Trainee from the Egyptian National Regulatory Authority (ENRA), National Organization for Research and Control of Biologicals, Egypt, July 2009
A trainee from the Egyptian National Regulatory Authority (ENRA) spent one week at the PEI in different areas of the WHO Collaborating Centre (CC).

The training comprised:
Coagulation factors, albumin and other blood products
Practical demonstrations
- Factor VIII-chromogenic test
- Factor V-clotting test
- Antithrombin – chromogenic test
- Prekallikreinactivator – chromogenic test

Tutorials on

- European network of Official Medicines Control Laboratories (OMCLs)
- EU batch release procedure of blood products and medical devices
- National batch release of blood products
- QM system

Immunoglobulins, immunosera, monoclonal antibodies and immunochemistry
Practical demonstration
- Potency test for anti-D
- Iso-electric focusing
- Protein composition by zone electrophoresis

Tutorials on
- Potency test for monoclonal antibodies
- Immunoelectrophoresis
- Quality Control charts
- Sample management.

11.2 Trainee from the Regional Blood Bank of Omsk, Russia, May 2010
A trainee from the Russian blood bank spent four days at the PEI Collaborating Centre and received training in the following:
Coagulation factors, albumin and other blood products
Tutorials on
- European network of Official Medicines Control Laboratories (OMCLs)
- EU batch release procedure of blood products and medical devices
- National batch release of blood products
- QM System

Practical demonstration
- Coagulation analyser BCS-XP.

Haemovigilance and vigilance of in vitro diagnostic (IVD) medical devices
Information on
- National haemo- and tissue- vigilance system
- Adverse events/reactions reporting system
- Classification and evaluation of reported serious transfusion/ transplantation reactions (communicating with physicians and manufacturers)
- German Haemovigilance Report
- Measures to improve safety standards/ Graduated Plan Procedure
- Blood donor screening
- Evaluation of screening tests
- European vigilance system
- Incidence report

European IVD Vigilance System
- Incident reporting system
- Classification and evaluation of reported incidences (by communicating with users, manufacturers, laboratories)

The trainee also spent time in the PEI-IVD Testing Laboratory.

11.3 Visitor from the Korean Red Cross, June 2010
A colleague from the National Red Cross of the Republic of Korea spent two days at the PEI discussing the evaluation of viral blood screening tests (serological and nucleic acid tests) and the quality control (batch release) of blood products.

11.4 Visitors to the PEI WHO Collaborating Centre

Delegation from the Shanghai Institute for Food and Drug Control (SIFDC), September 2009
A delegation of the SIFDC visited the PEI in September 2009. The colleagues from China were informed about the activities of the Section Batch Release of Blood Products, Logistics and later toured

the laboratories.

Delegates from the Mongolian Ministry of Health, the Shastin Hospital and the National Center of Communicable Diseases, October 2009
At the invitation of the German Ministry of Health, a delegation from Mongolia, including Dr Khurelbaatar Nyamdavaa, the Secretary of State for Health, at the Mongolian Ministry of Health visited the PEI. Both the German and Mongolian ministries had previously signed a bilateral agreement vowing to strengthen collaborations in the field of health. The delegates requested that staff should visit the PEI in the future for additional training for blood screening assays for hepatitis C virus (HCV). HCV is a particular problem in Mongolia and it is estimated that around 10% of the population are infected with the virus.
The regulation of blood products in Germany and the German WHA initiative were discussed. A tour of the blood products batch release testing laboratories was undertaken.

Visit of Delegates from the Chinese State Food and Drug Administration (SFDA), the National Institute for the Control of Pharmaceutical and Biological Products (NICPBP), the Center for Drug Evaluation (CDE), and the China Center for Pharmaceutical International Exchange (CCPIE), December 2009
The guests from China were interested in the marketing authorization of monoclonal and polyclonal antibodies at both the national (i.e., Germany) and the European level. The presentation on the regulation of blood products was well received. A laboratory tour followed, which comprised the blood products batch release testing area and the IVD testing laboratories.

Delegation from the National Institute for the Control of Pharmaceutical and Biological Products (NICPBP), March 2010
The delegation was headed by Dr Wang, Deputy Director of NICPBP. He was accompanied by Professor Dong, Head of Division Virus I, Professor Ye, Deputy Head of Division Bacteria I and Dr Li, Deputy Head of Division Virus III. Information was exchanged on vaccines and allergens, as well as alternatives for animal testing, quality control of blood products, and cord blood stem cells. There was also extensive discussion of new gene therapy developments. Both agencies agreed on closer cooperation and mutual support in order to establish new WHO collaborating centres.

Open Days at the PEI and the German Ministry of Health
The involvement of PEI, as a CC of the WHO, was included in the presentations at both open days. The global relevance of blood products and the work on behalf of the WHO was of particular interest to visitors, especially at the Ministry in Berlin.

Activity 12 Contribution to the development of guidelines and recommendations

Explanation

Two guidelines were in the focus of the centre's interest in 2009:

WHO Guideline on Good Manufacturing Practice for Blood Establishments
The International Conference of Drug Regulatory Authorities (ICDRA), Bern, Switzerland, 2008 had recommended that the WHO prioritize the development of a WHO Guideline on GMP for Blood Establishments.
This guideline is currently being drawn up by a drafting group. Dr Gerd Werner from PEI is member of the group. He presented the project to the audience of the ECBS in 2009 (plenary session) during his secondment to WHO from October 2008 until October 2009. The first draft was presented in the Blood Track as an information document (Info doc. 2). The revised version will be presented at the ECBS meeting in October 2010 for adoption. For more details see Activity 9.

Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs), WHO/BS/09.2110
The so-called Biosimilars Guideline draft was presented for the first time at the EBCB meeting in October 2008. As described in the last annual report, the guideline provoked discussion worldwide and PEI had expressed its concerns.
At the ECBS meeting in October a revised version was presented. As a consequence of the discussions, vaccines and plasma derived products were excluded from the scope of the guideline. The new draft was adopted by the Committee.

Activity 13 Development of an International Hepatitis C virus (HCV) Core Antigen Standard

Explanation

Global importance: HCV is distributed world-wide and is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. Globally, an estimated 170 million people are chronically infected by the virus, with an estimated 3 to 4 million new cases each year. A relatively high proportion of these people have no access to HCV testing, especially not HCV core antigen assays or HCV NAT tests (viral load determination).

Rationale: Highly sensitive qualitative and quantitative assays for the detection of HCV core, as well as HCV antigen/antibody combination assays have recently become available. The assays show a sensitivity and specificity comparable with those of commercially available viral load assays. They correlate well with these assays and appear to be suitable for large-scale screening of blood donations and for monitoring the therapeutic efficacy of HCV treatment. Thus, HCV core antigen assays may be an alternative to NAT HCV-RNA quantification.
Intended use: 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 HCV core reference material for the evaluation of improved tests or new devices.
Actions: A proposal was presented at the WHO Collaborating Centres Meeting in February 2009 and was subsequently endorsed by the ECBS in 2009. Currently HCV core antigen positive material is being sourced and characterized in terms of antigen content, correlation with HCV RNA and analysis of genotype in order to determine its suitability for use as a standard. To this end PEI has established contacts with various blood transfusion services and industry in order to obtain sufficient material for the preparation of an International Standard. One important parameter to validate is the stability of the HCV core antigen because preliminary results suggest that the stability at +4°C is lower than for, e.g. HBsAg and HIV p24 antigen. The ECBS in 2010 will be asked to support PEI in the search for a suitable amount of HCV core antigen material (0.5-1.0 litre of plasma is expected to be sufficient).
Outlook: Once sufficient material has been obtained, a feasibility study will be performed to investigate the suitability of the preparations. Once the material has been shown to be fit for purpose, then the collaborative study will commence before submission of the final report to the ECBS.

2. Other information related to the Collaboration between the centre and WHO. Briefly describe visits by WHO staff to the centre, visits by the centre staff to WHO (HQ and/or Regional Office), use of the centre staff by WHO, support provided by centre staff for courses cosponsored or organized by WHO (HQ and/or Regional Office), WHO financial support to the centre through contractual or Technical Services Agreement or other type of support provided by WHO, any other collaborative activities. Please mention any difficulties encountered in the collaboration and suggestions for increased and improved collaboration with WHO.

2.1 WHA Resolution 63.12 on Availability, Safety, and Quality of Blood Products
The PEI provided scientific input and support for a WHA resolution on the availability, safety, and quality of blood products. The PEI, represented by Professor Seitz, worked closely with the German Ministry of Health, which proposed the topic for the agenda of the WHO Executive Board (EB). According to the European Treaty, the subject falls within the community responsibility and the proposal for a WHA resolution was submitted by the 27 European Union member states and Serbia to the WHO Executive Board (EB) at the 125th meeting in May 2009. After very positive comments from several EB members, the proposal was endorsed at the 126th EB meeting in January 2010. The PEI representatives provided continuous input throughout the discussions, and advice to the German Ministry and the EU representatives during the development of the document. Finally, the resolution WHA63.12 was adopted by the Sixty-Third World Health Assembly; the text is available on the WHO website: http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R12-en.pdf.

2.2 60th ECBS Meeting, Geneva, Switzerland, 19 – 23 October 2009
PEI activities as a WHO Collaborating Centre are closely linked to the ECBS. The report on the activities

of the WHO Collaborating Centre (CC) for Quality Assurance of Blood Products and in vitro Diagnostic Devices was presented by Professor Rainer Seitz. He emphasized the new responsibilities of PEI for tissues and advanced therapy medicinal products. Professor Seitz told the committee members that Professor Klaus Cichutek was to become the new president of PEI.
In his talk, Professor Rainer Seitz also informed the audience about the German initiative for a World Health Assembly (WHA) resolution on the availability, safety, and quality of blood products (see above).
Professor Johannes Löwer, member of the ECBS and Dr Volker Öppling (for the Vaccines Track) also participated in the plenary session on the first day.
The new proposals of the PEI CC were presented by Dr Micha Nübling during the Blood Track sessions. Dr Thomas Montag-Lessing presented the Transfusion-Relevant Bacterial Strain Panel project. All new project proposals of the PEI CC were endorsed by the Committee.

At the 2009 meeting, the ECBS established the following guidelines:
- Guidelines on evaluation of similar biotherapeutic products (see above, Activity 12).
- Revision of current WHO Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines.
- Revision of current WHO Recommendations to assure the quality, safety and efficacy of live attenuated influenza vaccines.

Further items discussed included:
- Good manufacturing practices for Blood Establishments (see above, Activity 12).

Establishment of HBV DNA Panel
The summary report of the 2009 ECBS meeting highlighted the establishment of the 1st WHO International Genotype Panel for Hepatitis B Virus Nucleic Acid Amplification Technique (NAT) –Based Assays (see Activity 4). As the panel covers the most prevalent Hepatitis B genotypes (A-G) worldwide, it is expected to facilitate the detection of relevant genotypes by all countries as well as to improve the quality of Hepatitis B diagnostic devices.
Outcomes from the 2009 ECBS meeting are available as follows:
http://www.who.int/biologicals/expert_committee/ECBS2009_outcomes_for_website.pdf

2.3 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 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 59 INN requests of biological substances from June 2009 to June 2010. She attended two consultations of the INN expert group (49th and 50th consultation in November 2009 and May 2010, respectively) where all comments were discussed and decisions on the selection of INNs were taken.

2.4 Cooperation with WHO in the area of in vitro diagnostics (IVD): WHO prequalification programme for IVD
In August 2009, Dr Gaby Vercauteren and Irena Prat, WHO headquarters/ Diagnostics and Laboratory Technology (DLT)/ Department Essential Health Technologies (EHT) visited the institute in order to discuss possible cooperation in the WHO IVD prequalification programme for IVD. A confidentiality agreement has been signed and the collaboration commenced in May 2010.
The WHO programme focuses on the certification of rapid assays for the detection of HIV and malaria. PEI obligations include: (a) dossier reviews; (b) the contribution to the development of a guidance document on options for a quality assurance policy for procurement of HIV, TB and malaria

diagnostics; (c) review and provision of suggestions to a draft procedure for fast tracking of product dossiers for prequalification of diagnostics; (d) preparation and organization of meetings and workshops etc. Dr Vercauteren also made a request for secondments from the PEI; however these are currently not possible.

Respective Agreements for Performance of Work (APW) will be signed by both parties.
Dr Gabriele Unger attended the 5th Consultative Stakeholder Meeting on the UN Prequalification of Diagnostics, Medicines & Vaccines, Geneva, Switzerland on the 11th of February 2010.
A workshop on prequalification of HIV viral load assays (NAT) has since been organized by PEI (15 – 16 June 2010). At this meeting, criteria and work associated with the prequalification procedure were agreed between the testing laboratories which will be involved in this work.

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

2.5.1 IPFA/PEI 17th Workshop on Surveillance and Screening of Blood Borne Pathogens, Zagreb, Croatia, 26 – 27 May 2010
PEI co-organizes annual scientific meetings, primarily on the topics of application of nucleic acid amplification tests (NAT) and other measures to increase blood safety. These meetings are organized in close cooperation with the International Plasma Fractionation Association (IPFA). Standardization is included in the topics discussed at the congress. Dr Micha Nübling, Dr Julia Kreß, and Dr Sally Baylis participated in the workshop. Dr Baylis gave a talk on “Requirements for plasma screening – are our algorithms up to date and rational?”

2.5.2 SoGAT (Standardization of Gene Amplification Techniques) – Clinical Diagnostics II, Istanbul, Turkey, 30 Sep. – 1 Oct. 2009
Dr Chudy presented the proposal for a WHO project on the development of an international reference preparation for hepatitis D virus RNA.

2.5.3 Further conferences with CC relevant topics attended by PEI co-workers:
PDA (Parenteral Drug Association) Cell Substrate Workshop, Bethesda, USA, 29 – 30 Jul. 2009
Dr Sally Baylis, as the PEI representative, gave a talk on the “Regulatory Expectations of Validation/Qualification of Virus Assays”.
Koch-Metschnikow Conference (Russian-German Conference) on virus diseases and for coordination of joint projects on socially relevant diseases, Moscow, Russia, 17 – 18 Dec. 2009
PEI participant: Dr Micha Nübling.
2nd International Mycosafe Symposium, Vienna, Austria, 07 – 09 Apr. 2010
PEI participants: Dr Micha Nübling, Dr Thomas Montag-Lessing.
XXXIst International Congress of the ISBT (International Society of Blood Transfusion), Berlin, 26 Jun. – 01 Jul. 2010
PEI participants: Professor Rainer Seitz, Dr Thomas Montag-Lessing, Dr Micha Nübling, Dr Margarethe Heiden.

3. Collaboration with other WHO Collaborating Centres: Briefly describe the nature and outcome of the collaboration and the name(s) of the other WHO collaborating centre(s) with which the centre has collaborated. If applicable, please mention the name of the network of WHO CCs to which the centre belongs. Also include suggestions for increased and improved collaboration with other WHO CC

3.1 Collaboration with WHO Collaborating Centres for Biological Standardization
The PEI WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices works closely together with the two other WHO collaborating centres (CC) for biological standardization, the National Institute of Biological Standards and Control (NIBSC, UK), and the Center for Biologics Evaluation and Research, Food and Drug Administration (CBER/FDA, USA). Two meetings of the CCs have been held since the designation of the PEI CC. The last one was hosted by the Paul-Ehrlich-Institut in February 2009 (see last annual report).
The intention of the meetings is to agree on a list of priorities for future standardization projects, which are thereupon proposed to the ECBS. Regular telephone conferences are held prior to the ECBS and/ or when needed. Information about new developments and new proposals are given and a mutual basis for the ECBS is agreed upon.
Standardization projects for reference preparations are led by two or even the three CCs with increasing frequency (see Activities above, e.g. Activity 1). Since the organization of the collaborative studies is time and cost intensive and distribution of infectious materials is becoming more difficult, the allocation of work expedites the development of International Reference Preparations. This helps facilitate the distribution of the study materials more effectively.

3.2 Participation in collaborative studies (CS) of WHO International Blood Product Standards
The PEI laboratories of the section Batch Release of Blood Products, Logistics took part in several collaborative studies in 2009. The proposed candidate WHO International Standard (IS) materials were processed according to guidelines for the production of WHO IS at NIBSC, UK. These WHO IS are now / will soon be available for the calibration of secondary standards, as well as commercial reference preparations in order to improve inter-laboratory harmonization worldwide.
The results were in good agreement with other participating laboratories.

Collaborative Study	Organized by	Remarks
8th IS FVIII Concentrate	NIBSC	Stability Study
6th IS FVIII-vWF Plasma	NIBSC	Stability Study
1st IS C1-Esterase Inhibitor Concentrate	NIBSC	

3.3 Meetings organized by other Collaborating Centres
Dr Sally Baylis visited the Division of Hematology, CBER/FDA, Bethesda, USA, on 28 July 2009. She gave a presentation on “Parvovirus Contamination of Plasma: Detection of Novel Viruses and Genetic Variants”.

3. 4 Cooperation with the National Institute of Infectious Diseases (NIID), Japan
In May 2010, a delegation visited the institute under the direction of Dr Isao Hamaguchi, the director of the Department of Safety Research on Blood and Biological Products. The guests were interested in discussing PEI projects for the establishment of WHO Reference Preparations and other topics relevant for the quality and safety of blood products.
The main issue was the development of the WHO International Standard for Hepatitis E Virus RNA for Nucleic Acid Amplification Technique (NAT)-based Assays which will be developed in close cooperation with the NIID (see Activity 2).