Collaborating Centres
PROGRESS REPORT

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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	07/2010 to 07/2011		

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

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, respectively).

A report on this study has recently been accepted for publication:
Baylis SA, Ma L, Padley DJ, Heath AB, Yu MW. Collaborative study to establish a World Health Organization International Genotype Panel for parvovirus B19 DNA nucleic acid amplification technology (NAT)-based assays. Vox Sanguinis, in press.

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 outbreaks of acute viral hepatitis cases in endemic areas (e.g. in Africa, Asia, Central America). High mortality rates of up to 25% occur in pregnant women and individuals with underlying liver disease. In industrialized countries HEV infection may be linked to travel to endemic areas, however autochthonous cases are increasing, with zoonotic transmission from swine and other species. HEV viraemia and faecal shedding occur several weeks prior to the development of anti- HEV IgM and IgG.

It is now recognized that HEV diagnostic testing, including NAT, is important in patients where other causes of acute hepatitis have been excluded. Transfusion transmission of HEV occurs and the virus is relatively resistant to viral inactivation/removal procedures, consequently NAT screening has been proposed for certain classes of plasma-derived products with limited virus reduction steps. Vaccines against HEV are under development. It is anticipated that the standard will be used by clinical laboratories, particularly hepatitis reference laboratories, as well as blood banks, plasma fractionation organizations and associated control laboratories.
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 was proposed to develop the genotype 3a strain as the candidate International Standard and the genotype 3b strain as the candidate Japanese national standard. The candidate standards were lyophilized in August 2010 and the collaborative study has been performed in conjunction with the Japanese National Institute for Infectious Diseases (NIID). For the collaborative study, coded duplicate samples of the two strains were distributed to participating laboratories; genotype 3a HEV (Samples 1 and 2) and genotype 3b HEV (Samples 3 and 4). The samples were assayed on 4 separate occasions and the data were collated and analysed at the PEI. The study involved 23 laboratories from 10 countries. All assays were able to detect both candidate standards. The combined mean estimates for the 2 candidate standards were: 5.60 log10 copies/ml (quantitative NAT); 5.26 and 5.29 log10 NAT-detectable units (qualitative NAT end-points) for strains 3a and 3b, respectively. Based upon the combined data, both preparations were estimated to have a potency of 5.39 log10 units/ml. Participants used plasmid DNA, synthetic oligonucleotides, and in vitro transcribed RNA containing HEV sequences to control for copy number. Other controls included calibrated plasma and stool samples. No standard method was used, and this is reflected in the variation observed for the quantitative results (in the order of 2 log10) which was improved by expressing results relative to Sample 1 as a standard. For the qualitative assays, variation in NAT-detectable units was >3 log10, and again, expressing potencies relative to Sample 1, improved the agreement between the different laboratories and methods. The genotype 3a HEV strain is proposed as the candidate International Standard and will be considered for establishment by the ECBS at the annual meeting in October 2011.

The results of the initial phase of the study have recently been published:
Baylis SA, Hanschmann KM, Blümel J, Nübling CM. (2011) Standardization of hepatitis E virus (HEV) nucleic acid amplification technique (NAT)-based assays: an initial study to evaluate a panel of HEV strains and investigate laboratory performance. Journal of Clinical Microbiology, 49, 1234-1239.

Activity 3 Transfusion-Relevant Bacterial Strain Panel

Explanation

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

Previously, no international bacterial references existed in order to perform low titre spiking experiments for the objective validation and comparison of bacteria detection methods and PRT. Therefore, the International Society of Blood Transfusion (ISBT) Working Party Transfusion-Transmitted Infectious Diseases (WP-TTID, chair: Dr Silvano Wendel), Subgroup on Bacteria (chair: Dr Thomas Montag-Lessing), organized an international study on Transfusion-Relevant Bacteria References (TRBR) to be used as a tool for development, validation and comparison of both bacterial screening and pathogen reduction methods.
Four TRBR were blinded and distributed to 14 laboratories in 10 countries for identification, enumeration and proliferation analyses in PCs after low titre spiking (0.3 and 0.03 CFU/ml). Thirteen laboratories returned data concerning bacterial counts and identity; twelve laboratories returned data on the growth ability of the strains. The results of the study demonstrated the stability of the TRBRs and consistency of results in a large number of transfusion laboratories all over the world.

In 2009, the 2nd Meeting of the WHO Collaborating Centres to Support the Development of WHO Biological Reference Preparations for Blood Safety-related in vitro Diagnostic Tests recommended submission of the study results to the WHO ECBS for review. Following the advancements in this field aiming to establish a recognized reference for worldwide use were discussed during the annual meetings of ECBS in 2009 and 2010.

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

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

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

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

Explanation

The proposed 1st International Reference Panel for HBV genotypes (PEI code number 5086/08), intended for use with HBV NAT assays, consists of 15 lyophilized HBV positive plasma samples which cover the most prevalent HBV genotypes A to G worldwide, was established by the ECBS in October 2009 (WHO/BS/09.2121). The panel is held at PEI and is available on request.

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

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 proposal was endorsed by WHO ECBS in October 2009. The project is being undertaken in close cooperation with the Institute of Hepatology, Ankara University, Turkey and with the Institute for Medical Virology, Justus von Liebig University in Giessen, Germany. One of the outcomes/needs from the EASL (European Association for the Study of the Liver) Monothematic Conference Delta Hepatitis held in Istanbul, Turkey in September 2010 were that EASL strongly support the standardization efforts. The type of standard proposed (i.e. HDV diluted in human plasma, analogous to the other WHO NAT standards for blood borne viruses) would be suitable for all current NAT methods. The proposed standard preparation will consist of 2000 – 4000 vials containing approximately 105 copies HDV-RNA/vial. The fill volume 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. Two HDV RNA-high titre plasma samples (HDV-1) with a sufficient volume, provided by the Institute of Hepatology of the Ankara University, were characterized in a feasibility study in Dec. 2010/Jan. 2011 to evaluate their suitability as candidates for further development in the preparation of the international standard. The study was performed by five different laboratories in Germany with expertise in molecular diagnosis of HDV. The laboratories used different HDV NAT systems. The study results demonstrated that the two potential candidate materials had a viral load ranging from 3.0 x105 – 5.3 x108 copies/ml and 2.7 x105 – 6.4 x107 copies/ml, respectively. The reason for the striking differences in the concentration of the HDV RNA is not yet clear, but emphasizes the urgent need for standardization is this field. In order to investigate this further, well characterized HDV RNA transcripts comprising all target regions will be investigated in a second study. An international collaborative study will subsequently be conducted to evaluate the candidate reference materials. The final report is expected to be submitted to the ECBS in July 2012 for establishment of the 1st International Standard for HDV RNA.

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

Explanation

This task is coordinated by the ISTH SSC (International Society on Thrombosis & Haemostasis/ Scientific and Standardization Committee) Working Party on Factor XIII Standardization (Chair: Prof. Akitada Ichinose, Yamagata University, Japan). Unfortunately, due to difficulties of participating laboratories to allocate resources to this work, there was no progress in the past year. The PEI continues to be interested in establishing the 1st International Standard for factor XIII concentrate.

Activity 7 Exploration of a new factor VIII potency assay

Explanation

There are discrepancies between results of the chromogenic and the one-stage clotting potency assays which appear most pronounced when FVIII activity is measured in immuno purified Factor VIII (FVIII) and B-domain deleted products.
The one-stage clotting assays are used for clinical purposes and product labelling e.g. in the USA. However, the European Pharmacopoeia (Ph. Eur.) prescribes the chromogenic assay for potency determination, and anticipates that in the case of recombinant FVIIIs, product-based reference materials, the activity of which is determined relative to the international standard, will be used.

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

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

PEI experts continue to work in advisory groups including the Ph. Eur. expert group 6B, the EMA Biologics Working Party, and committees in scientific societies, e.g. the International Society on Thrombosis & Haemostasis (ISTH) in order to explore possibilities to optimize existing test methodology as well as new alternatives, with the aim to harmonize FVIII potency measurement in a way suitable for both clinical and regulatory purposes.

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

Explanation

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

Activity 9 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

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 during the reporting period.

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 2010, this meeting took place on the 21st of October. Unfortunately, both PEI representatives were unable to travel to Geneva due to other pressing issues, but participated during part of the session by telephone conference. Further BRN telephone conferences were held on 29 Jun., 8 Nov. 2010, 24 Jan., 28 Feb., and 9 May 2011.
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 was present and explained the Japanese interest in participating in the BRN. A dialogue was established between the BRN and the Japanese authorities and the Japanese representative will be invited to the next face-to-face meeting during 2011 ECBS. Since the current BRN Terms of Reference do not allow inclusion of new Members, the BRN decided to prepare a draft amendment of the Terms of Reference for consideration of the ECBS and WHO Secretariat, since other WHO member states may be interested in joining the group.

A major focus of the BRN in the past year was 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. During the 2010 ECBs meeting and telephone conferences thereafter, the document Assessment Criteria for Evaluation of Blood Regulatory Systems was finalized; it was posted on the BRN web site http://www.who.int/bloodproducts/brn/en/ and was presented during ICDRA 2010 in Singapore.

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 web site, and documents produced by the BRN for publication are posted on the above mentioned web site.

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 and control of blood products. This is also in line with the WHA Resolution 58.13 / Report EB113/10 and the most recently adopted WHA Resolution on Availability, Safety and Quality of Blood Products (WHA Resolution 63.12, May 2009).

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

The availability of WHO fellowships may assist in training costs.

11.1 Trainees from the Health Sciences Authority (HSA), Singapore, 27 Sep. – 1 Oct. 2010
Trainees from the Egyptian National Regulatory Authority (ENRA) spent one week at the PEI visiting the respective areas of the WHO Collaborating Centre..
One of the colleagues attended training on:
"Immunoglobulins, immunosera, monoclonal antibodies"
•Licensing of immunoglobulins, immunosera, monoclonal antibodies
oNational procedure
oEuropean procedure (centralized)
oEuropean procedure (decentralized = mutual recognition)
oCommunication via Eudra-Track and EudraNet
•Clinical trial authorization
•European Pharmacopoeia requirements
oGeneral
oActivities regarding development of test methods and standards
•Relevant Guidelines
•Dossier evaluation: Presentation of a current assessment report
oQuality
Immunoglobulins
Monoclonal antibodies
Immunosera
• GMP-inspections
•Batch release
oOMCL system and general principle
oQuality assurance
Running the system (procedures, database)
Handling of OOS-results
Validation of analytical methods
Validation of potency methods
Internal and external quality control
Qualification of photometric equipment
Qualification of flow cytometry (FACS)
oMeasures taken in case of defect batches
oPotency tests
Anti-D
Anti-tetanus
Anti-HAV
Anti-HBsAg
Anti-ATG
Anti-rabies
Monoclonal antibodies
oPKA, ACA and Fc-function test
oChemical analysis
Al- and Hg-determination by AAS
Protein determination (280 nm, Biuret, Kjeldahl)
Osmolality
Residual moisture
TNBP by GC
Chloride, formaldehyde, phenol
oImmunochemical analysis
Identity Testing (Ouchterlony)
Immunoelectrophoresis
oBiochemical analysis
Ion exchange chromatography
Size exclusion chromatography
SDS-PAGE
Iso-electric focussing
Protein composition by zone electrophoresis.

Advanced therapy medicinal products (ATMPs), which include for examples gene therapy medicinal

products, somatic cell therapy medicinal products, and tissue-engineered products, are of increasing importance and present special regulatory challenges. Two of the trainees spent time in the PEI division Medical Biotechnology to become familiar with German procedures concerning ATMPs:
•Regulatory Background
oNational and European legal provisions
oWorking parties, Guidelines
oScientific advice procedure
oEvaluation and approval of clinical trials
oClassification of medicinal products
•Specific medicinal products incl. case studies of licensed products
oNon-viral gene transfer medicinal products
oViral gene transfer medicinal products
oTissue engineered medicinal products
oCell therapy
oTissue preparations
oXenogenic therapy

Three further colleagues from the HSA spent a week at PEI in May 2010 covering different aspects of ATMPs. One of the visitors stayed for a further three weeks in the division in order to receive more in depth training.

11.2 Trainee from the Safe Blood Transfusion Project in Pakistan, 21 Feb. – 9 Mar. 2011
A technical officer from the Safe Blood Transfusion Project of the Pakistani Ministry of Health in collaboration with the "Deutsche Gesellschaft für Technische Zusammenarbeit" (GTZ, German Technical Cooperation, now GIZ, Deutsche Gesellschaft für Internationale Zusammenarbeit, German Company for International Cooperation) spent two weeks at the institute to undertake training in the following areas:
"The European regulatory system for biologicals and the Quality Management System (QMS) at the Paul-Ehrlich-Institut"
•Licensing of biological / biotechnological medicinal products
oEuropean procedure (centralized)
oEuropean procedure (decentralized, mutual recognition)

•QMS at PEI
oRequirements of ISO 17025
oQMS structure and functions
oControl of documents
oReview of applications, assignments and contracts
oSubcontracting tests
oPurchasing equipment, material and services
oProcessing inquiries
oControl of non-conforming tests
oRecords
oReview of the QMS
oQualification of personnel
oValidation of tests
oHandling of test samples and reference materials
oAssuring quality of test results

•Audit system
oTraining of auditors
oAudit programme
oAudit plan
oAudit practice

"Bacterial safety and pyrogen testing"
•Sterility control
oSterility testing of biologicals according to Ph. Eur. 2.6.1

oAutomated computer controlled sterility testing
oSterility control of blood components
oRegulations in sterility control of blood components
oAlternative methods for detection of bacteria in blood components
oDifferentiation and characterization of bacteria, including PCR-fingerprinting

•Pyrogen Testing
oPyrogen testing, Ph. Eur. 2.6.8
oBacterial endotoxin testing (LAL), Ph. Eur. 2.6.14
oPyrogen testing by human whole blood assay
"Viral safety"
•Viral safety of blood products and recombinant products; dossier evaluation; interpretation of virus validation studies and application of EU Guidelines

"Virus testing / In vitro diagnostic (IVD) test kits"
•IVD Directive 98/79/ EC (IVDD)
oBasic elements, essential requirements, standards, IVD classification, conformity routes, common technical specifications (CTS), notified bodies, competent authorities, CE certification
oSerological assays (dossier evaluation with special emphasis on the diagnostic evaluation; common technical specifications (CTS), dossier evaluation, assessment report
oNAT (Nucleic Acid Amplification Techniques) assays (dossier evaluation: e.g. design of the assay, diagnostic evaluation, CTS, quality control (QC); conformity with IVDD requirements; assessment report)
•Batch verification of manufactured products according to the IVDD (overview on the procedures and samples used; establishment of verification criteria, assessment of QC documents)
oSerological assays
oBlood grouping devices
oNAT assays
•Plasma pool testing
oTesting for anti-HIV and HBsAg by serological methods
oDetection of HCV-RNA, B19-DNA by NAT
•Viral safety testing of biologicals
oDesign and establishment of NAT methods, validation, control
•Validation of NAT (Nucleic Acid Amplification Techniques) assays
oGuidelines, requirements, procedures; assessment of NAT validation documents
•Practical exercises
oPhysical testing of serological assays (sample preparation, methods, test report)
oPhysical testing of NAT assays (extraction, amplification, detection; sensitivity, linear range, controls, NAT methods, test report)

"Pharmacovigilance II", Haemovigilance
•National Vigilance System
oAdverse drug reactions reporting system
oLook-back procedure
oIncident reporting systems
oNational Pharmacovigilance Database (E2B Standard)
oCorrective actions – Graduated Plan
oPeriodic safety update report (PSUR)
•European Vigilance System
EU communication
Non urgent information (NUI)
Rapid alert (RAS)

11.3 Visitors to the PEI WHO Collaborating Centre
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 Beijing Drug Administration (BJDA), the Beijing Institute for Drug Control, the China Center for Pharmaceutical International

Exchange (CCPIE), and several local Drug Control Authorities, Nov. 2010

Marketing authorization of biologicals and the procedure for the approval of clinical trials in Germany was discussed with the Chinese delegates. The European system for CE-marking of in vitro diagnostic devices was another topic on the agenda.

Activity 12 Contribution to the development of guidelines and recommendations

Explanation

As mentioned before (Activity 9), the WHO Guideline on Good Manufacturing Practice (GMP) for Blood Establishments was adopted by the Expert Committee on Biological Standardization in October 2010 (WHO/BS/10.2139).

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

Explanation

Hepatitis C virus (HCV) is distributed worldwide and a major cause of acute and chronic liver disease, including cirrhosis and liver cancer. Globally, an estimated 170 million people are chronically infected with HCV and there are 3 to 4 million new infections each year. A relative high number of these persons do not have access to appropriate HCV testing. The virus is highly variable and six major genotypes (comprising numerous subtypes) with distinct geographical distributions have been described.

Rationale: Highly sensitive qualitative and quantitative HCV core-detection assays as well as HCV antigen/antibody combination assays have become available recently. The HCV core antigen assays in particular, show comparable performance to commercially available viral load assays and thus appear to be suitable for screening of blood donations and for monitoring the therapeutic efficacy of antiviral treatment. HCV core antigen assays may represent a reasonable alternative to HCV RNA NAT-based assays (detection quantification) and thus may contribute to the improvement of health and blood safety.

Intended use: An HCV core antigen reference preparation will be useful for the quality control of test kits by regulatory organizations and for standardization of HCV antigen quantification in routine clinical diagnostics. Manufacturers can use HCV core reference material for the evaluation and development of improved HCV antigen detection tests or new devices, and for validation purposes.

Actions: A proposal was presented at the 2nd WHO Collaborating Centres Meeting in February 2009 at the PEI and was subsequently endorsed by the ECBS in 2009. In 2010-2011, the focus was on the sourcing of suitable starting materials which could be used in both HCV core and the less sensitive HCV antigen/antibody combination tests. Several candidate materials were collected from German blood banks, the National Institute for Biological Standards and Control (NIBSC), the Institute of Haematology and Transfusion Medicine in Warsaw, Poland as well as from US sources. The samples were analysed for HCV antigen concentration and the correlation with the RNA content, the HCV genotype and the absence of antibodies to HCV. A few samples would have been acceptable but were of limited supply. Nevertheless, a suitable sample was finally identified. The material was collected from a single US blood donor in 1996 and was drawn on two occasions, two days apart. The sample contains a genotype 1 HCV strain which is of benefit since this genotype has one of the broadest geographical distributions worldwide. The material is currently undergoing further evaluation and characterization. The studies will also include an investigation of the stability of the HCV core antigen, since preliminary evidence suggests that it might be lower than that of other antigens used in screening assays. In addition, lyophilization of the material will be evaluated to ascertain whether it retains its immunological properties after freeze-drying.

Outlook: Upon successful completion of these characterization studies, the final formulation and filling of the candidate standard will be performed. Subsequently, a collaborative study will be undertaken to establish a WHO International Standard.

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 61th ECBS Meeting, Geneva, Switzerland, 18 – 22 October 2010
PEI activities as a WHO Collaborating Centre (CC) are closely linked to the ECBS. The report on the activities of the WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices was presented by the new President of the Paul-Ehrlich-Institut, Professor Klaus Cichutek. Besides his description of the PEI CCs work plan activities he summarized the efforts of the institute concerning the World Health Assembly (WHA 63.12) resolution on the availability, safety, and quality of blood products.
He informed the committee that Germany currently has a member on the Executive Board. The representative is Dr Ewold Seeba from the Ministry of Health. The German priorities in collaboration with WHO currently relate to:
•strengthening of public health systems and
•the quality and safety of medicines.

Professor Cichutek also described the new activities of PEI colleagues in the WHO Prequalification Programme of in vitro Diagnostics (see 2.4).

Dr Micha Nübling, rapporteur of the Blood Products Track of the ECBS meeting, and Dr Volker Öppling (for the Vaccines Track) also participated in the plenary session on the first day.

Dr Nübling made a new proposal to establish an International Standard for mycoplasma for NAT-based assays. The ECBS committee members endorsed the proposal (see also 2.3).

Dr Thomas Montag-Lessing presented the final report of the Transfusion-Relevant Bacterial Strain Panel project. The panel was adopted by the Committee as the WHO Transfusion-Relevant Bacterial Strain Repository. However, the Committee requested the final version of the instructions for use, which was submitted to WHO in February 2011 (see also Activity 3).

Dr Sally Baylis from PEI had commented on WHO/BS/10.2138: Collaborative Study to Evaluate the Proposed 1st WHO International Standard for Human Cytomegalovirus (HCMV) for Nucleic Acid Amplification (NAT)-Based Assays.
An important point raised by Dr Baylis was the commutability which has not been fully addressed by WHO IS collaborative studies so far. A discussion about the comments took place when the HCMV standard project was presented and the commutability issue is under further discussion with a meeting planned early in the New Year to develop a WHO guideline.

Dr Gerd Werner attended the meeting in order to finalize the WHO Guideline on Good Manufacturing Practice (GMP) for Blood Establishments (WHO/BS/10.2139) following the comments after the presentation on the second day.

At the 2010 meeting, the ECBS established the following guidelines which are relevant to the work of the Collaborating Centre:
•WHO Guideline on Good Manufacturing Practice (GMP) for Blood Establishments (WHO/BS/10.2139) (see also above, Activities 9 and 12).
•Model guidance for the storage and transport of time and temperature–sensitive pharmaceutical products (WHO/BS/10.2129).
•Update on the WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies (WHO/BS/10.2152).

Reference Preparations established by the 2010 ECBS meeting have been published on the WHO Biologicals web site as follows (download):

http://www.who.int/biologicals/Reference_preparations_established_by_ECBS.pdf

The report includes the adoption of the Transfusion-Relevant Bacterial Strain Repository. It consists of preparations of four bacteria strains: Staphylococcus epidermidis, Klebsiella pneumoniae, Streptococcus pyogenes, and Escherichia coli.
Final versions of the approved documents are/ will also available on the WHO Biologicals web site: http://www.who.int/biologicals/expert_committee/en/.

2.2 International Conference of Drug Regulatory Authorities (ICDRA), Singapore, 30 November – 3 December 2010
Professor Klaus Cichutek, President of PEI and Dr Uwe Unkelbach, Head of Section Batch Release of Blood Products attended the first two days of the 14th International Conference of Drug Regulatory Authorities.

Workshop A: Blood and Blood Products

Klaus Cichutek gave a presentation on the "Regulation of Advanced Blood Cell Therapies". This topic is gaining more interest worldwide with clinical trials being performed in many countries. Stem cell research and clinical applications are being actively investigated. Specific regulations concerning ATMPs were introduced in the European Union in 2007 (1394/2007/EC) and provide an example of regulations supporting the development of innovative medicines.
The main topics of his lecture were:
•clinical trials using cell-based products
•substantially manipulated cells and cells for non-homologous use
•quality, safety and non-clinical aspects
•the future.

In the same session, the Blood Regulators Network (BRN) gave an update on the activities of the group. The document "Assessment Criteria for Evaluation of Blood Regulatory Systems" was presented at the meeting. It is available on the BRN web site http://www.who.int/bloodproducts/brn/en (see also Activity 10).

Professor Cichutek also chaired the Workshop E on Pandemic H1N1: Lessons Learned.

2.3 Establishment of an International Standard for Mycoplasma NAT
PEI Project leaders: Micha Nübling, Thomas Montag-Lessing
In October 2010 the WHO Expert Committee on Biological Standardization (ECBS) endorsed the project proposal to establish a WHO International Standard (WHO IS) for Mollicutes ("Mycoplasma") NAT. The Paul-Ehrlich-Institut was asked to conduct this project.

An international reference material for Mollicutes NAT is expected to be an important tool for the standardization of different nucleic acid tests designed for the detection of Mycoplasma contamination of biological materials and/or for diagnosis of Mycoplasma infections. NAT testing for Mycoplasma contamination plays an increasing role in the safety testing of biological materials used for the production of biological products, including biological medicines. Furthermore, regulatory authorities in different regions of the world increasingly accept Mycoplasma NAT testing as a replacement for (or in combination with) culture-based Mycoplasma detection methods. A WHO IS for Mycoplasma NAT will be useful for:
•standardizing NAT assays of different design with a common material;
•performing validation of different methods with the use of a common material;
•reporting quantitative test results by different assays in a common unitage (International Units/ml), and expressing analytical parameters (e.g. limit of detection) in a common unitage.
Prior to the establishment of the candidate material, a feasibility study will be performed to evaluate different candidate materials, to determine the current consistency of result reporting by different assays and to investigate the suitability of a future WHO IS.

Since adoption of the project the preparation for the feasibility study has been undertaken. A call for

interest has been published in close cooperation with the Parenteral Drug Association (PDA) Mycoplasma Task Force. Manufacturers and users of NAT assays are also being contacted directly to assure global representation of participants. NAT assays to be included in this study should be designed to detect a variety of different Mollicutes species (including e.g. Mycoplasma pneunomiae, Mycoplasma fermentans, Mycoplasma orale, and Acholeplasma laidlawii) which again may be included as members of the feasibility panel. Initial feedback has shown that there is widespread interest in standardization of Mycoplasma NAT assays.

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

INNs are assigned to a range of biologicals including recombinant blood products, monoclonal antibodies and gene therapy medicinal products which fall under the responsibility of the PEI.
Dr Weißer assessed 56 INN requests of biological substances from July 2010 to June 2011. She attended two consultations of the INN expert group (51st and 52nd consultation in November 2010 and April 2011, respectively) where all comments were discussed and decisions on the selection of INNs were taken.

2.5 Cooperation with WHO in the area of in vitro diagnostics (IVD): WHO prequalification programme for IVD
The PEI collaboration with the WHO/ Diagnostics and Laboratory Technology (DLT)/ Department Essential Health Technologies (EHT) started in May 2010 after a confidentiality agreement had been signed.
From 2010 to June 2011 the WHO programme focused on the prequalification of rapid assays for the detection of HIV and malaria. PEI´s contributions included participation in: (a) dossier reviews; (b) site inspections; (c) input into the development of guidance for reviews, and elaboration of a draft procedure for fast tracking of product dossiers for prequalification of diagnostics; and (d) the preparation and organization of a workshop on HIV NAT.

Dr Sigrid Nick and Dr Micha Nübling attended WHO dossier assessors meetings on prequalification of HIV and malaria tests organized by WHO on 24 – 25 Jun. and 11 – 13 Oct. 2010. At these meetings, checklists, criteria and assessment outcomes associated with the prequalification procedures were discussed and agreed between the assessors who will be involved in the programme. Dr Nübling chaired the meeting in October.

From October 2010 to June 2011 Heiner Scheiblauer and Sigrid Nick participated in site inspections of the prequalification programme carried out at four manufacturers of HIV and malaria rapid tests in the United States, South Korea and Japan. In addition, eight HIV rapid test dossiers have been received since September 2010 and it was possible to review seven of these by June 2011.

An Agreement for Performance of Work (Reg. File P17-APW-099) for the review of dossiers and the organization of the meeting as well as the contribution to the development of the guidance document was signed in July 2010.

2.6 WHO Global Forum for Blood Safety - Patient Blood Management, 14 – 15 March 2011, Dubai, United Arab Emirates
This WHO Global Forum for Blood Safety - Patient Blood Management was attended by Dr Uwe Unkelbach. It is part of the WHO Blood Transfusion Safety Programme.

Dr Neelam Dhingra, WHO/ Blood Transfusion Safety (BTS) / Department Essential Health Technologies (EHT) is the coordinator of the group. Experiences from blood transfusion settings around the world were shared with the plenary. More than 100 participants attended the forum, including representatives from 41 developed and developing countries: national blood programme managers, international clinical and transfusion medicine experts, public health experts, academicians, hospital administrators, as well as representatives of the WHO Expert Advisory Panel on Transfusion Medicine, WHO Collaborating Centres, WHO headquarters and regional offices, other UN organizations (UNFPA, UNAIDS, UNDP and UNICEF) and key international non-governmental and professional organizations working on clinical blood use and blood safety.

In his presentation Dr Unkelbach gave an overview on the "WHO Collaborative Activities conducted by PEI". There was great interest in the PEI blood products batch release procedures and results.

2.7 2nd International Congress on Transfusion Medicine-Plasma Industry, 10 – 11 May 2011, Tehran, Islamic Republic of Iran
This 2nd International Congress on Transfusion Medicine and Plasma Industry was successfully organized by the Iranian Blood Transfusion Organization (IBTO). More than 400 participants from 15 different countries including Iran, Syria, Pakistan, Iraq, Turkey, Tajikistan, Kyrgyz Republic, Jordan, Egypt, Austria, the Netherlands, France, Germany, United Kingdom, and Malaysia.

Speakers of internationally well-known organizations like the International Society of Blood Transfusion (ISBT), the International Plasma Fractionation Association (IPFA), the Plasma Protein Therapeutics Association (PPTA), and WHO gave presentations on various aspects of plasma-derived medicines. Whilst these products are life-saving, their biological nature presents particular safety challenges. The treatments are used for a range of rare and serious diseases.
Dr Unkelbach gave a presentation on the "Role of stakeholders; NRA and fractionators in plasma fractionation" and gave an overview of the Paul-Ehrlich-Institut's experience of experimental batch release of these products over the last 15 years.

This congress highlighted the importance of accessibility of safe and high quality plasma derived medicines to patients throughout the world.

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

2.8.1 IPFA/PEI (International Plasma Fractionation Association) 18th Workshop on Surveillance and Screening of Blood Borne Pathogens, Dublin, Ireland, 24 – 25 May 2011
PEI co-organizes this annual scientific meeting, the primary focus concerns the application of nucleic acid amplification tests (NAT) and other measures to increase blood safety. These meetings are organized in close cooperation with the International Plasma Fractionation Association (IPFA). Standardization is one of the topics discussed regularly at the congress. Dr Micha Nübling, Dr Michael Chudy, Dr Thomas Montag-Lessing and Dr Sally Baylis participated in the workshop. Dr Nübling gave an update on the recent SoGAT (Standardization of Gene Amplification Techniques) meetings on clinical diagnostics and blood testing and Dr Montag-Lessing made a presentation on screening strategies for human cells, tissues, and cellular and tissue-based products for transplantation.

2.8.2 SoGAT (Standardization of Gene Amplification Techniques) – Clinical Diagnostics III, Institute of Child Health, London, UK, 12 – 13 Jan. 2011
The International SoGAT Clinical Diagnostics Working Group is focused on the standardization of NAT (Nucleic Acid Amplification Technology) assays used in the diagnosis of clinical pathogens. The principle remit of the group is to prioritize and coordinate the development of reference preparations for clinically relevant pathogens and to encourage discussion on assay performance and technology issues. Dr Micha Nübling, Dr Michael Chudy and Dr Julia Kreß attended the meeting. Dr Nübling gave a presentation about the new project for the establishment of the first WHO International Standard for Mycoplasma NAT, which was endorsed by the ECBS meeting in Oct. 2010. He also gave an overview of revisions to the European IVD Directive 98/79/EC – impact on clinical diagnostics. Dr Chudy presented

an "Update on the development of an International Standard for HDV RNA".

2.8.3 SoGAT: XXII Scientific Working Group on the Standardization of Genome Amplification Techniques for the Safety Testing of Blood, Tissues and Organs for Blood-borne Pathogens. Rome, Italy, 14 – 15 Apr. 2011
Dr Micha Nübling and Dr Michael Chudy attended the meeting and gave two presentations each.
Dr Nübling presented an "Update on the development of an mycoplasma reference panel" and "Cases of HIV-1 RNA non-detection and their potential impact on NAT design";
Dr Chudy gave an "Update on the development of the 1st international standard for HEV RNA" as well as an "Update on the development of the 1st International Standard for HDV RNA".

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

XXVIII Annual Scientific Meeting of the British Blood Transfusion Society, Bournemouth, UK, 9 – 11 Sep. 2010.
PEI Participant: Dr Melanie Störmer

EASL (European Association for the Study of the Liver) Monothematic Conference Delta Hepatitis, Istanbul, Turkey, 24 – 26 Sep. 2010.
PEI Participant: Dr Michael Chudy. Presentation: Towards standardization of HDV RNA measurement.

Extraordinary meeting of the International Society of Blood Transfusion (ISBT) Working Party Transfusion-Transmitted Infectious Diseases (WP-TTID), Subgroup on Bacteria. American Association of Blood Banks (AABB) Annual Meeting, Baltimore MD, USA, 9 – 12 Oct. 2010.
PEI Participants: Dr Thomas Montag, Dr Melanie Störmer

Global harmonization conference, National Institute of Standards and Technology (NIST), Gaithersburg, USA, 26 – 27 Oct. 2010.
PEI Participant: Dr Micha Nübling.
Dr Nübling led one of the breakout sessions of the meeting on situational/gap analysis. The conclusions from the meeting have recently been published in Clinical Chemistry: Roadmap for Harmonization of Clinical Laboratory Measurement Procedures. Miller WG, Myers GL, Lou Gantzer M, Kahn SE, Schönbrunner ER, Thienpont LM, Bunk DM, Christenson RH, Eckfeldt JH, Lo SF, Nübling CM, Sturgeon CM. Clin Chem. 2011 Aug;57(8):1108-17. Epub 2011 Jun 15.

VII All-Russian Scientific-Practical Conference "Molecular Diagnostics". Moscow, Russia, 24 – 26 Nov. 2010.
PEI Participant: Dr Micha Nübling, made presentations on Blood Safety Testing and Standardization of Molecular Diagnostics.

European GMP Education Course Validation of Molecular Biological Methods. Vienna, Austria, 8 – 9 Feb. 2011.
PEI Participant: Dr Micha Nübling. Presentation on International Standards for Biological Targets.

21. Meeting of the German Society for Virology. Freiburg, Germany, 23 – 26 Mar. 2011.
PEI Participant: Dr Micha Nübling. Presentation on Blood screening NAT tests for HIV-1 group M require two different target regions.

Sanquin Spring Seminar 2011: Advances in clinical transfusion science, Amsterdam, The Netherlands, 14 – 15 Apr. 2011.
PEI Participant: Dr Melanie Störmer.

Plasma Product Biotechnology Meeting 2011. Paphos, Cyprus, 9 – 13 May 2011.
PEI Participant: Dr Micha Nübling. Presentation on Emerging viral variants may impact testing strategies.

21st Regional Congress of the International Society of Blood Transfusion (ISBT), Lisbon, Portugal, 18 – 22 Jun. 2011.

PEI Participants: Dr Thomas Montag, Dr Melanie Störmer.

Plus
Working Party on Transfusion-Transmitted Infectious Diseases. 21st Regional Congress of the ISBT. Lisboa, Portugal, 18 – 22 Jun. 2011.
PEI Participant: Dr Micha Nübling. Presentation on Blood screening HIV-1 NAT test failures - International surveillance of NAT / serology discordant screening test results.

Parenteral Drug Association (PDA) European Virus and Transmissible Spongiform Encephalopathy (TSE) Safety Forum, Barcelona, Spain, 27 – 30 Jun. 2011.
PEI Participants: Dr Johannes Blümel. Dr Blümel gave a presentation on "Reduced viral clearance data for biotech and plasma derived products".

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 Third Meeting of WHO Collaborating Centres to support the development of WHO Biological Reference Preparations (BRP) for blood products and in vitro diagnostic devices (IVD), National Institute for Biological Standards and Controls (NIBSC), Potters Bar, UK, 7 – 8 Mar. 2011

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).

The Quality Assurance and Safety: Blood Products and Related Biologicals (QSD) Team within the unit of Quality Assurance and Safety of Medicines (QSM), Department for Essential Medicines and Pharmaceutical Policies (EMP), WHO headquarters invited members from the collaborating centres to attend the 3rd meeting of the WHO Collaborating Centres, which was held at NIBSC.

The intention of these meetings is that the three CCs agree on future standardization projects, which are subsequently proposed to the ECBS. Telephone conferences may also be held prior to the ECBS meetings.

Dr Julia Kreß, Dr Thomas Montag-Lessing, Dr Micha Nübling, Dr Heiner Scheiblauer and Dr Gabriele Unger attended the meeting on behalf of PEI.

Dr Phil Minor, NIBSC, who chaired the meeting, welcomed the participants. Dr Ana Padilla of WHO/ QSD gave an overview the WHO biological reference preparations (BRPs) for the control of quality and safety of blood products, the WHA Resolution 63.12 on Availability, Safety and Quality of Blood Products and the consequences of the resolution.

A discussion on commutability of WHO BRPs followed. It was agreed to follow up this issue with a meeting of experts. The commutability of BRPs to clinical samples has not been investigated widely in WHO studies. NAT standards, which might be of synthetic origin, will be considered further in the near future by the WHO CCs. A guideline will be drafted to help address how commutability can be investigated during evaluation of BRPs during collaborative studies.

The current projects, new proposals and the priorities of standardization projects were presented by the project leaders of the three CCs and other participants. Julia Kreß of PEI gave an overview on the development of the 1st International Standard for HDV RNA. Heiner Scheiblauer gave an update on the progress of the HCV core antigen standard project. Micha Nübling reported the results from the collaborative studies of the HBsAg subtype panel as well as the 1st International Standard for HEV RNA. The panel as well as the standard will be proposed for establishment by the ECBS in October 2011. The extension of the WHO Transfusion-Relevant Bacterial Strain Repository, which was established by the ECBS in 2010 was described by Thomas Montag-Lessing and discussed by the audience. Concern had been raised by the ECBS that the strains are not lyophilized. This may be an

issue for countries without guaranteed cold chain transport and storage. Although such kind of samples is not excluded as WHO BRPs, the preference is for the lyophilization of all biological standards. It was agreed lyophilized samples will be included in the new study.

The proposal to meet annually was considered, since there is growing interest in the outcomes of the CC meeting by other organizations, including laboratories and manufacturers of IVDs. The outcome of the meeting will be presented to the ECBS in October 2011. The report will be provided on the WHO web site: http://www.who.int/bloodproducts/en/index.html.

3.2 Participation in collaborative studies of WHO International Blood Product Standards
The Batch Release of Blood Products, Logistics section of PEI participated in several collaborative studies in 2010. 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 upon collaborative studies, which the PEI participated in, the WHO Expert Committee on Biological Standardization (ECBS) established the following WHO International Standards (IS) in 2010:

Collaborative Study(all studies organized by NIBSC, UK)
1st IS C1-Inhibitor, Concentrate (08/256)
1st IS C1-Inhibitor, Plasma (08/262).

The results were in good agreement with other participating laboratories.

PEI was also involved in other collaborative studies conducted during 2010:
•Stability study for the 2nd IS for von Willebrand Factor, Concentrate. The studies for the value assignment of the proposed standard had already been carried out in 2009.
•Collaborative study for the value assignment of the 2nd IS for Fibrinogen, Concentrate. The report for the study is still pending.
•Collaborative study for the value assignment of the 3rd IS for Fibrinogen, Plasma. The report for the study is still pending.

PEI also took part in international collaborative studies to establish secondary plasma standards:
•ISTH/SSC (International Society on Thrombosis & Haemostasis/ Scientific and Standardization Committee) Secondary Coagulation Plasma Standard Lot #4.
PEI carried out assays to calibrate the reference preparation for:
-Protein C Function
-Protein S Function
-Factor XI Function
-Factor V Function
-Factor VIII Clotting Activity
-Factor VIII Chromogenic Activity
-vWF Ristocetin Cofactor Activity
-vWF Collagen Binding Activity
-vWF Antigen
-Fibrinogen Function
-Factor XIII Activity
The report for the study is still pending.

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 three studies to replace WHO International standards for blood borne viruses. The following standards will be submitted to ECBS in October 2011 for establishment.

Collaborative Study (all studies organized by NIBSC, UK)
HCV RNA (06/102); Proposed 4th IS

HBV DNA (10/264); Proposed 3rd IS
HIV-1 (10/152); Proposed 3rd IS.