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**Name of the University, Hospital, Research Institute, Academy or Ministry**

Paul-Ehrlich-Institute (PEI)

**Name of the Division, Department, Unit, Section or Area**

Division of Haematology and Transfusion Medicine

**City** Langen **Reference Number** DEU-117

**Title** WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices

**Report Year** 07-2015 to 07-2016

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

**Activity 1**

Title: Development of an International Standard for Hepatitis B Virus e Antigen (HBeAg).

Description: It is proposed to prepare an international HBeAg standard to evaluate HBeAg assay analytical sensitivity. It may also serve for calibration of secondary standards by manufacturers of diagnostic kits, for quality control by competent authorities and by users. The participants of the collaborative and commutability study include reference laboratories for viral hepatitis, public health laboratories, competent authorities and IVD manufacturers developing HBV assays that are located worldwide.

20 laboratories contribute to establish an overview of assay sensitivity over a range of countries covering Europe (France, Germany, Netherlands, United Kingdom, Russia), America (Canada, USA, Brazil), and Asia (Thailand, China, Korea, Japan, Russia). Thirteen different assays covering different assay formats (ELISA, ChLIA, RIA and ECL) are used.

Annette Reissinger, Sigrid Nick

The standard was adopted by the Expert Committee on Biological Standardization (ECBS) as the "1st WHO International Standard for Hepatitis B Virus e Antigen (HBeAg)" in October 2013.

Stability studies are ongoing.

**Activity 2**

Title: Development of a WHO International Standard for Antibodies to Hepatitis B Virus e Antigen (anti-HBe-IgG)

Description: The Paul-Ehrlich-Institut (PEI) anti-HBe IgG-material has been used since 1982 for calibration of the anti-HBe kits and many manufacturers have referred the sensitivity to PEI units. There is continuous demand for this anti-HBe standard. Human plasma positive for anti-HBe-IgG in high titres, has been characterized to establish the international standard. The value assignment in IU will be performed in an international collaborative study involving reference laboratories, test kit manufacturers and competent authorities from worldwide.

The anti-HBe-IgG international standard will be used for determination of the analytical sensitivity of anti-HBe assays. It may also serve for calibration of secondary standards by manufacturers for their test kits, for quality control by competent authorities and by users.

Olivia Knauer, Heiner Scheiblaue

The “1st WHO International Standard for anti-hepatitis B virus e antigen (anti-HBe)” was adopted by the ECBS in October 2013.

Stability studies are ongoing.

### **Activity 3**

Title: Development of a WHO International Standard for Hepatitis C virus (HCV) Core Antigen

Description: A HCV core antigen standard would be especially useful for estimating the sensitivity of HCV core antigen assays and of HCV antigen/antibody (Ag/Ab) combination assays. It may also serve for calibration of reference materials by manufacturers of diagnostic kits.

First qualitative and quantitative HCV core antigen assays intended to be used for blood screening and / or for HCV patient monitoring have already been introduced into the market. In addition, also HCV Ag/Ab combination assays have become available now. For comparable antigen detecting assays, such as HBsAg (Hepatitis B Virus surface antigen) or HIV-1 p24 (Human Immunodeficiency Virus capsid antigen) tests, the availability of internationally recognized standard preparations has been of great value and the correlation between analytical and clinical sensitivity is well established. Such preparations have proven essential for manufacturers for standardizing their devices. Regulatory bodies benefit from such materials for the assessment of the sensitivities or failures of devices. Even users take advantage of international reference preparations for selecting high quality devices. The benefit for HCV infected patients will be the availability of improved HCV core assays for monitoring the virus load and thus optimized anti-viral therapy.

Sigrid Nick, Heiner Scheiblaue

The “1st WHO International Standard for Hepatitis C virus (HCV) Core Antigen” (HCV Ag, PEI code 129096/12) was adopted by the ECBS in October 2014.

Stability studies are ongoing.

### **Activity 4**

Title: Development of a WHO International Standard for Hepatitis D Virus RNA

Description: For the preparation of the standard material several HDV RNA-positive plasma samples representing the most predominant clade HDV-1 were provided by the Institute of Hepatology, Ankara University, Turkey in 2010. A feasibility study was performed involving several laboratories to characterize the materials and to find out the suitable candidate material for the standard preparation. The lyophilized standard preparation will be evaluated in a worldwide collaborative study.

The HDV RNA International Standard will be used by clinical diagnostic laboratories, IVD manufacturers and NCLs for the development and calibration of NAT assays, for the calibration of secondary references and working standards, and for the evaluation of standardized preparations used in quality control and quality assurance.

Michael Chudy

In October 2013, the ECBS established the material (PEI code 7657/12) as the 1st WHO International Standard for HDV RNA for NAT based assays with an assigned potency of  $5.75 \times 10^5$  International Units per mL (IU/mL) when reconstituted in 0.5 mL of nuclease-free water. Stability studies are ongoing conforming to the requirements of the establishment of WHO international reference preparations. Further follow-up investigations will be performed to underpin the commutability of the WHO material.

### **Activity 5**

Title: Development of a WHO International Genotype Panel for Hepatitis E Virus (HEV) RNA for Nucleic Acid Amplification Technique (NAT)-based assays

Description: The need for standardization of NAT assays for HEV RNA was initially demonstrated in the first ever international proficiency testing study coordinated by the Paul-Ehrlich-Institut. In a follow-up study, the 1st International Standard (IS) for HEV was established by the Expert Committee on Biological Standardization (ECBS) in October 2011.

The IS has been prepared from a genotype 3a HEV strain, obtained from a Japanese blood donor. HEV can be classified into at least four main genotypes. Genotypes 1 and 2 can be found in humans, whilst genotypes 3 and 4 are found in both humans as well as a range of animal species, particularly pigs and wild boar where the sequences between the animal and human strains, circulating in the same geographic region, are closely related with evidence for zoonotic infection.

The geographical distribution of HEV genotypes is complex. Genotype 1 consists of strains circulating in Africa and Asia (Egypt, Algeria, Morocco, Sudan, and Chad; India, Pakistan, Nepal, Bangladesh and China). Genotype 2 is found in Mexico and in some African countries (Nigeria, Namibia, Chad, and Sudan). Genotype 3 is widely distributed, mainly being reported in the USA, Europe and Japan. Genotype 4 is restricted to India and East Asia. However, genotype 1 viruses, and more recently genotype 4 viruses, are found in patients in Europe, North America and elsewhere after travelling to endemic areas and represent imported cases. Epidemics and sporadic cases of hepatitis E occur in areas of endemicity (genotypes 1, 2 and 4); more isolated clinical cases occur among a sizeable group of mostly asymptomatic seropositive residents in developed countries (genotype 3). It is now well recognised that genotype 3 HEV can cause chronic infection in transplant patients with monitoring of viral loads in response to antiviral therapy.

From sequence analysis of different HEV strains, at the nucleotide level, there is in the order of 74% nucleotide identity between genotypes. In the case of genotype 3 for example, there are at least 10 sub-genotypes which vary by up to 15% nucleotide identity. In order to ensure appropriate coverage of NAT assays for HEV, the availability of a genotype panel would be a valuable tool.

A panel of different HEV genotypes and important sub-genotypes will be evaluated by a group of laboratories including reference laboratories for viral hepatitis, public health laboratories, blood banks/plasma fractionation organizations, control laboratories, research laboratories and organizations developing vaccines and IVD manufacturers developing HEV NAT assays. The panel samples will be evaluated alongside the WHO IS. Such a panel will be valuable to ensure adequate detection of HEV from both human and zoonotic sources.

Sally Baylis

At the annual meeting of the WHO ECBS in October 2011, the proposal was made by the PEI to develop an international reference panel for hepatitis E virus genotypes. The ECBS endorsed the proposal. A panel of HEV-positive samples, comprising eleven different members including genotype 1a (2 strains), 1e, 2a, 3b, 3c, 3e, 3f, 4c, 4g as well as a human isolate related to rabbit HEV, has been lyophilized between August 2013 and August 2014. A collaborative study was initiated in November 2014; the aim was to evaluate the panel against the “1st WHO International Standard (IS) for HEV RNA” (code number 6329/10). Also included in the study was a candidate Biological Reference Preparation (BRP) for HEV RNA prepared from an HEV 3f virus strain on behalf of the European Directorate for the Quality of Medicines and HealthCare (EDQM). The samples for evaluation were distributed to 24 laboratories from 14 different countries. The samples were assayed on three separate days and the data were collated and analysed at the PEI. Data were returned by 23 of the participating laboratories. In total 32 sets of data were returned; 17 from quantitative assays and 15 from qualitative assays. The assays used consisted of a mixture of in-house developed and commercially available assays. The results showed that all samples were detected consistently by the majority of participants. It is proposed that the panel, consisting of 11 members, be established as the “1st WHO International Reference Panel (IRP) for all HEV genotypes for NAT-based assays” (code number 8578/13) with no unitage being assigned to the individual panel members; the study report has been reviewed by the ECBS in October 2015. In the case of the candidate BRP, a unitage of 40,850 IU/ml (4.6112 log<sub>10</sub> IU/mL) has been assigned to the material after calibration against the WHO IS. Real-time stability studies have indicated that the panel of HEV samples and the candidate BRP are very stable under normal conditions of storage, i.e., at -20°C or below, and are therefore suitable for long term use. Ongoing real time stability studies of the panel members and the BRP are in progress.

The WHO International Reference Panel was established by the ECBS as the “1st WHO International Reference Panel for Hepatitis E Virus Genotypes” in October 2015.

The BRP was adopted by the European Pharmacopoeia Commission in February 2016.

Stability studies are ongoing.

#### **Activity 6**

Title: Extension of the 1st WHO Transfusion-Relevant Bacterial Strain Repository

Description: 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-P-06), *Klebsiella pneumoniae* (PEI-B-P-08), *Streptococcus pyogenes* (PEI-B-P-20), and *Escherichia coli* (PEI-B-P-19).

(Störmer, M. et al. International Validation Study on Blood Transfusion Bacteria Standards Relevant to Transfusion Medicine-ISBT Working Party Transfusion-Transmitted Infectious Diseases (WP-TTID), Subgroup on Bacteria. *Vox Sang* 10-2011) (ISBT = International Society of Blood Transfusion).

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

An enlargement of the repository was requested and agreed by ECBS (2010).

The list of 21 bacterial candidate strains was discussed during the annual meetings of WP-TTID, Subgroup on Bacteria San Diego 2011 and Cancun 2012). As an outcome a list of 11 selected bacterial strains was proposed which includes spore forming bacteria (*Bacillus* spp. spores) as well as coagulase-negative *Staphylococcus* (CNS), *Klebsiella*, *Pseudomonas*, *Streptococcus*, *Salmonella* and *Serratia* species. These strains had been produced by PEI. After stability testing and sequencing of bacterial 16srRNA the 11 candidate strains as well as the four approved reference strains will be included in the planned enlargement study and distributed to the participating laboratories for testing in platelet concentrates (under real life conditions) regarding their ability to proliferate in platelet concentrates after low spiking (< 1 CFU/ml). The study will be divided in 2 phases and will be performed in different regions of the world.

The Transfusion-Relevant Bacterial Strain Panel will be available to blood banks and manufacturers of approaches for improvement of bacterial safety of blood worldwide. Furthermore it will allow regulatory agencies to decide on those approaches in an objective and standardized manner.

Eva Spindler-Raffel

Platelet Transfusion Relevant Bacteria Reference Strains, which are provided as ready to use, deep frozen suspensions in a defined cell count, are a feasible tool for validation and assessment of various microbiological methods for improving blood safety. Neither resuspension nor cultivation is needed prior to use. In the second collaborative study, 11 candidate strains were characterized. Those that demonstrate growth independently of donor effects under "real life" conditions were recommended for inclusion in the WHO International Reference Repository of Platelet Transfusion Relevant Bacterial Reference Strains.

The 11 candidate strains, which were finally included in the collaborative study, are as follows:

Gram-negative species: *Enterobacter cloacae* PEI-B-P-43, *Morganella morganii* PEI-B-P-74, *Proteus mirabilis* PEI-B-P-55, *Pseudomonas fluorescens* PEI-B-P-77, *Salmonella cholerae-suis* PEI-B-P-78, *Serratia marcescens* PEI-B-P-56.

Gram-positive species: *Staphylococcus aureus* PEI-B-P-63, *Streptococcus dysgalactiae* PEI-B-P-71, *Streptococcus bovis* PEI-B-P-61 (*Streptococcus bovis* is currently named *Streptococcus gallolyticus* due to phylogenetic results). Aerobic spore forming bacteria: *Bacillus cereus* spores PEI-B-P-07-S, *Bacillus thuringiensis* spores PEI-B-P-57-S.

The study protocol included the enumeration of inoculum and low spiking of test bacteria directly in PC bags (inoculum concentration 10 to 25 CFU per PC bag). Growth kinetics were documented by sampling and enumeration after storage on days 2, 4 and 7.

The 15 strains were shipped on dry ice to the 14 collaborating laboratories (Austria 1, Canada 1, England 1, Germany 3, Japan 1, Mexico 1, Pakistan 1, South Africa 1, The Netherlands 1 and USA 3), which finished the corresponding tests in June 2014. Stability testing of all investigated strains was performed routinely at PEI during the study period and beyond until April 2015. The identity of the bacteria strains was verified by a combination of classical and molecular microbiological procedures. Classical characteristics included growth properties, colony morphology, Gram-staining, and biochemical parameters like metabolism of certain sugars (API-System). Additionally, part of the 16s ribosomal RNA gene was sequenced.

The individual growth curve kinetics showed variation from slow to fast growth. *Bacillus cereus*, *Bacillus thuringiensis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas fluorescens*, *Serratia marcescens*,

*Staphylococcus aureus* and *Streptococcus dysgalactiae* showed a growth of significantly more than 2 log<sub>10</sub> CFU/mL up to 8 log<sub>10</sub> CFU/mL by day 2 of storage. For *Enterobacter cloacae*, *Proteus mirabilis*, *Staphylococcus epidermidis*, *Streptococcus bovis* (reclassified *Streptococcus gallolyticus*) and *Streptococcus pyogenes* this growth level was reached at day 4. Growth for *Salmonella choleraesuis* was lower than for the other strains and showed a high variability among the results of the different participants. In addition, the study provided information regarding the growth behaviour and kinetics of different bacterial species in PCs. *Morganella morganii* PEI-B-P 74 failed to grow beyond that amount of bacteria in the initial inoculation. As *Morganella morganii* caused transfusion incidents in the past (i.e. US, FDA 2014), it was decided to qualify another strain of this species. In an additional study, eight partners tested a second strain in accordance with the study protocol as a proposal for replacing the *Morganella morganii* strain from the main study. It was recommended to add *Morganella morganii* PEI-B-P-91 to the bacteria extension list. The results of the collaborative study were presented to the TTID WP at several meetings (i.e. ISBT Congress Seoul, June 2014, extraordinary meeting TTID WP subgroup on bacteria Philadelphia, October 2014 and ISBT Regional Congress London June, 2015). The study report was sent to the WHO in June 2015 (WHO/BS/2015.2269). According to the results, WHO ECBS adopted 10 candidate strains including *Morganella morganii* PEI-B-P-91 for the WHO Repository of Platelet Transfusion-Relevant Bacterial Reference Strains.

The panel now consists of 14 strains held and distributed by the PEI:

Type of standard PEI Code number Bacteria strain

1st WHO International Repository for Platelet-Transfusion Relevant Bacterial Reference Strains 8483/13

*Staphylococcus epidermidis* PEI-B-P-06

*Streptococcus pyogenes* PEI-B-P-20

*Escherichia coli* PEI-B-P-19

*Klebsiella pneumoniae* PEI-B-P-08

Enlargement of WHO International Repository for Platelet-Transfusion Relevant Bacteria Reference Strains

11162/16 *Bacillus cereus* PEI-B-P-57 (spore suspension)

11163/16 *Bacillus thuringiensis* PEI-B-P-07 (spore suspension)

11164/16 *Enterobacter cloacae* PEI-B-P-43

11165/16 *Morganella morganii* PEI-B-P-91

11166/16 *Proteus mirabilis* PEI-B-P-55

11167/16 *Pseudomonas fluorescens* PEI-B-P-77

11168/16 *Serratia marcescens* PEI-B-P-56

11169/16 *Staphylococcus aureus* PEI-B-P-63

11170/16 *Streptococcus bovis* PEI-B-P-61 (reclassified *Streptococcus gallolyticus*)

11171/16 *Streptococcus dysgalactiae* PEI-B-P-71

#### Literature

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5 Montag T: Perspectives and limitations in the bacterial screening of platelet concentrate. *J Lab Med* 2006; 30: 60-65

6 Palaveino EL, Yomotovian RA, Jacobs MR: Bacterial contamination of platelets. *Transfusion Apheres Sci* 2010; 42:71-82

7 Störmer M, Arroyo A, Brachert J, Montag T. 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 Sang.* 2012; 102:22-31.

8 Müller B, Walter-Wenke G, Kalus M, Alt T, Bux j, Zeiler T, Schottstedt V: Routine bacterial screening of platelet concentrates by flow cytometry and its impact on product safety and supply. *Vox Sang.* 2015, 108 209-218.

9 Schrezeimer H, Walter-Wenke G, Müller TH. Et al: Bacterial contamination of platelet concentrates: results of a prospective multicenter study comparing pooled whole blood-derived platelets and apheresis platelets. *Transfusion* 2007; 47:644-652

10 Montag T: Strategies of bacteria screening in cellular blood components. Clin Chem Lab Med. 2008; 46:926-32.

11 Störmer M, Vollmer T. Diagnostic Methods for Platelet Bacteria Screening: Current Status and Developments. Transfus Med Hemother 2014; 41:19–27.

### **Activity 7**

Title: Development of a WHO International Standard for Mycoplasma Nucleic Acid Amplification Techniques (NATs)

Description: Mycoplasma nucleic acid amplification techniques (NATs) play an increasing role both in the testing of biologicals for contaminants and in the diagnosis of patients for bacterial infections.

The lack of standardization of Mycoplasma NATs impedes comparative assessment of the performance of different NAT systems, regulatory assessment of NAT systems and reporting of NAT test results in a “common language”.

Nucleic Acid Amplification Techniques (NATs) have been introduced as potential alternative methods in European Pharmacopoeia for the detection of Mycoplasma as part of the 2.6.7 monograph. Similar approaches have been chosen in the US where Mycoplasma NATs may be used for contamination testing of biological, after proper validation.

Micha Nübling

The candidate material was adopted by the ECBS as the “1st WHO IS for mycoplasma DNA for NAT assays, designed for generic mycoplasma detection”.

Stability studies are ongoing.

### **Activity 8**

Title: Participation in the Blood Regulators Network (BRN)

Description: The BRN is a working group of seven leading regulatory authorities in the field of blood products with the task of reacting rapidly to emerging risks, assessing new technologies, and providing advice to WHO. Professor Seitz had been the first chairperson of the BRN (2006 to 2008). Current topics are e.g. support for implementation of Resolution WHA63.12 and the BRN document “Assessment Criteria for National Blood Regulatory Systems”, assessment of new developments such as pathogen inactivation technology, discussion of opportunities for international convergence of regulations.

Rainer Seitz, Margarethe Heiden

End of July 2015, Margarethe Heiden retired and was replaced by Anneliese Hilger, who is the head of the section "Coagulation Products I" at the PEI and the current chairperson of the CHMP (Committee for Medicinal Products for Human Use) Blood Products Working Party of the European Medicines Agency. The BRN reported to the ECBS during the annual ECBS meeting at the WHO headquarters in Geneva and met for a closed meeting on Thursday, 15 October 2015. Furthermore, BRN telephone conferences were held on 10 September 2015, and on 28 January and 13 June 2016.

In March 2014, the BRN had provided the Position Paper on Collection and Use of Convalescent Plasma or Serum as an Element in Middle East Respiratory Syndrome Coronavirus Response. During the serious outbreak of Ebola in West Africa, the WHO secretariat had coordinated the organization of clinical trials aiming at the scientific evaluation of the so far experimental therapy option of convalescent whole blood (CWB) or plasma (CP). To this end, WHO convened an ad hoc working group including members of the BRN, which operated by regular telephone conferences. This ad hoc working group elaborated the document Interim Guidance for National Health Authorities and Blood Transfusion Services on the Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks, which was updated in April 2015. During its closed meeting on Thursday, 15 October 2015, the BRN was connected by video conference with Johan van Griensven, Institute of Tropical Medicine, Belgium, who presented results of Ebola clinical trials using convalescent plasma. The BRN appreciated this opportunity to have a discussion with Johan van Griensven, and expressed great esteem for his outstanding involvement.

The Ebola crisis dramatically increased the awareness for the importance of functioning national blood systems as part of the response to emergencies. In 2012, the BRN had provided the document Assessment Criteria for Evaluation of Blood Regulatory Systems. Another important milestone was the addition of blood and blood components to the WHO Model List of Essential Medicines. The BRN initiated its work on the development of a guidance document on the management of blood and blood components as essential medicines, which should also be an element of the implementation of national blood regulatory systems. The actual items of discussion as well as the minutes of BRN meetings and teleconferences are confidential. However, general information about the BRN and documents produced by the BRN for publication are available on the BRN website <http://www.who.int/bloodproducts/brn/en/>.

### **Activity 9**

Title: Support for the project "Improving Access to Safe Blood Products through Local Production and Technology Transfer of Technology in Blood Establishments"

Description: The project was started with the workshop "Improving Access to Safe Blood Products in Low- and Middle- Income Countries (LMIC): A Framework to improve Public Health" at WHO Headquarters, Geneva, 14 -15 June 2012. Professor Rainer Seitz and Dr Micha Nübling contributed presentations from PEI. The initiative is an important element in the implementation of Resolution WHA63.12, which has been supported also by the WHO BRN, e.g. by elaborating the document "Assessment Criteria for National Blood Regulatory Systems". PEI experts will contribute to drafting further guidance documents, and activities towards their implementation. Dissemination by relevant WHO departments, WHO Regional Offices; Government support for local manufacture of medical products.

Uwe Unkelbach, Rainer Seitz, Sabine Wegehaupt, Micha Nübling

As a follow-up to the workshops held in Jakarta, Indonesia in June 2014 (see Annual Report 2015), Dr Sabine Wegehaupt participated in the "WHO Workshop on Assessment of Good Manufacturing Practices (GMP) in Regard to Recovered Plasma in Blood Establishments" held in Surabaya, Indonesia from 10-14 August 2015. As part of the assessment team she evaluated the implementation of GMP at a pilot centre of the Indonesian Blood Transfusion Service (Surabaya Blood Center) during a 3 day visit. All activities were financed by the WHO.

### **Activity 10**

Title: Contribution to the Development of a WHO Technical Document on the Residual Risk in Blood Components

Description: The PEI has profound experience due to involvement in several national and international regulatory committees, including EMA (European Medicines Agency) working parties and expert groups of the European Pharmacopoeia, and scientific societies, such as ISTH, ISBT. Experts of the PEI, as desired and appropriate, will be ready to actively contribute to the elaboration and/or updating of guidance documents, such as the guidance on blood products in Technical Report Series, no. 840, and no. 932 (revision of the Recommendations for the Preparation, Characterization and Establishment of International and other Biological Reference Standards). Currently, a WHO Guideline on the residual risk in blood components is being drafted which may facilitate decision-making in regard to testing strategies for blood borne pathogens, taking the regional epidemiological background of the donor population into consideration.

Micha Nübling

The document was finalized in 2016 and submitted to ECBS for adoption as WHO Guideline on Estimation of Residual Risk of HIV, HBV or HCV Infections via Cellular Blood Components and Plasma.

### **Activity 11**

Title: Contribution to the Development of a WHO Technical Document on the Preparation and Calibration of Secondary Reference Preparations (IVD standards)

Description: The PEI has profound experience in the development of WHO International Standards for the in vitro diagnostic (IVD) area. An important task is the assurance of the continuity of the International Units for secondary standards. Currently, different approaches are obviously followed by different parties for the establishment and calibration of secondary standard preparations. A document is proposed which covers the steps and issues to be considered on the establishment of secondary standards.

Michael Chudy

At the last SoGAT meeting (Standardization of Gene Amplification Techniques, see 2.7.3) in London, UK, in June 2016 the final draft WHO Manual on the Preparation and Calibration of Secondary Reference Preparations (IVD standards) was discussed. The document will be updated by including all relevant comments from the meeting discussion and submitted to WHO for public consultation and adoption by the ECBS in October 2016.

### **Activity 12**

Title: Contribution to the Development of a WHO Technical Document on Commutability

Description: The PEI has profound experience in the development of WHO International Standards for the IVD area. These materials are used for standardization of different diagnostic assays. An important prerequisite for the proper use of these standards is their feature to be representative for routine clinical specimens, e.g. in regard to the analyte tested for or the test matrix (e.g. human plasma or serum). The representation of clinical specimens by a reference material is called commutability. If a reference material is non-commutable to clinical specimens, a bias may be introduced between different assays. Currently not all commutability aspects are fully addressed by the collaborative studies organized for the establishment of WHO International Standards.

Micha Nübling, Sally Baylis

Discussions between the WHO Collaborating Centres (WHO CCs) on addressing commutability issues during development of WHO reference materials took place at different occasions (e.g. SoGAT, see 2.7.3). In the meantime, it is common practice that at least few clinical samples are included into the collaborative study to compare the results for these specimens obtained by different assays with and without standardization. Though this approach may identify non commutable reference materials, it does not represent a full commutability study. However, there is now the common understanding between the WHO CCs that commutability needs to be addressed by either the collaborative study, separate studies, or by inclusion into proficiency testing programmes after establishment. Due to differences between WHO reference materials (some even originate from clinical specimens), and numbers of different assays to be included into collaborative studies further details of how exactly to address commutability have not been defined, for good reasons.

**Activity 13**

Title: Assuring safety and availability of blood products in developing countries: Good Manufacturing Practices (GMP) & Educational Tools for blood/plasma collection establishments

Description: This is an initiative to establish and implement GMP in blood establishments by the organization of meetings and training courses in several regions of the world, with presentations by experienced inspectors (including PEI), and attendance of pharmaceutical inspectors, heads of blood national programs and delegates from regulatory authorities in the respective nations/regions.

National/regional benefit: Optimal use of and benefit from donated blood plasma. Locally available essential blood plasma derived medicinal products. Incorporation of developing countries in the international transfusion community and associated industries.

Support to the quality control of blood safety related IVDs both serology and NAT.

Uwe Unkelbach, Sabine Heinz-Stempel, Sigrid Nick, Micha Nübling

This activity is closely linked with Activity 9 (see there).

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

2.1 66th Meeting of the Expert Committee on Biological Standardization (ECBS), Geneva, Switzerland, 12-16 October 2015

The president of the PEI, Professor Cichutek, depicted the recent activities of the WHO Collaborating Centre. He presented the work towards the development of a WHO International Reference Panel (IRP) for NAT-Based Assays of the Hepatitis E Virus (HEV) Genotypes as well as the development of a WHO IRP for anti-HEV antibodies. Both projects were presented for endorsement by the committee later during the meeting. Furthermore, Professor Cichutek also presented the progress on the enlargement of the first WHO International Reference Repository for Platelet-Transfusion Relevant Bacterial Strains by 11 further strains, which was later presented for establishment, and an additional project on a transfusion-relevant strain repository for red blood cells, which was presented for endorsement (see also resp. activities).

Professor Cichutek also reviewed additional ongoing activities of the PEI, including the participation in the blood regulators network (BRN), the contribution of PEI experts in the development of WHO technical documents (e.g. residual risk in blood components, secondary reference preparations), the support of PEI for the WHO project "Achilles (Improving Access to Safe Blood Products)", and the involvement of PEI in the regulatory systems strengthening activities of WHO.

At the end of this ECBS meeting, the committee adopted the 1st WHO International Reference Panel for HEV-RNA for Hepatitis E Virus Genotypes and endorsed the project to develop a WHO 1st International Reference Panel for anti-HEV. The committee encouraged the inclusion of genotype information.

Moreover, the committee endorsed both the extension of the 1st WHO Repository of Platelet Transfusion-Relevant Bacterial Reference Strains by 10 strains and the project to establish the 1st WHO Repository of RBC Relevant Bacteria Strains.

Dr Jens Reinhardt (PEI) shared the rapporteur ship for the blood/IVD track with Dr Clare Morris (NIBSC).

2.2 New Projects endorsed at ECBS Meetings

2.2.1 Development of an International Standard for IgG Antibodies to Human Cytomegalovirus (Anti-HCMV-IgG), endorsed by ECBS in 2013

Description Human Cytomegalovirus (HCMV) is spread worldwide with prevalence between 40% and 100%. The virus causes relatively mild and asymptomatic infections in immune competent persons, but can cause congenital disease and severe complications in those with immunodeficiency, e.g. immunological immaturity; acquired immunodeficiency or immunosuppression. Diagnostics of HCMV specific IgG and IgM antibodies and IgG avidity play a major role in prenatal care, blood transfusions and especially transplantation medicine.

Current anti-HCMV assays differ considerably in their sensitivity, and there is no international reference material available at the moment. PEI anti-HCMV-IgG reference material has been available since 1982, which is frequently requested by manufacturers for calibration of their anti-CMV test kits. But this material is of

limited supply and is weakly positive and not defined in international units. The proposed standard may serve for the calibration of the manufacturer's diagnostic kits, for quality control by competent authorities, and by users.

Nina Wissel, Dr Heiner Scheiblaue

The project to establish the "1st WHO International Standard for Anti-HCMV IgG" was endorsed by the ECBS in October 2013.

The candidate standard material is human plasma, highly positive for anti-HCMV IgG with high avidity and is anti-HCMV IgM negative to avoid interference with IgG. After lyophilization in 2013, 1900 ampoules were obtained. A collaborative study initiated in 2013 included (I) the candidate material, (II) the PEI anti-HCMV-IgG reference material, (III) a commutability panel with eight anti-HCMV positive samples with various IgG avidity levels and various anti-HCMV-IgM titers, as well as (IV) 50 human plasma samples negative for anti-HCMV-IgG and IgM to check specificity. The collaborative study included 15 laboratories from seven countries worldwide comprising reference laboratories, manufacturers and users. Overall, 16 different anti-HCMV-IgG assays of various test formats and principles were used. A potency of about 47 IU per ml could be assigned to the candidate material in order to evaluate the analytical sensitivity of anti-HCMV IgG assays and to improve comparability of results between laboratories.

The evaluation of study results and statistical analysis, as well as the preparation of the report is still ongoing in 2016. Submission of the report of the collaborative study to ECBS is planned for 2017.

### 2.2.2 International Anti-Hepatitis E Panel Description

The diagnosis of HEV requires a variety of tests including the detection of IgM and IgG antibodies. Analysis of IgM antibodies is particularly useful for the confirmation of acute infection. Anti-HEV IgG may also be detectable during acute infection. Anti-HEV IgG is also a marker of past HEV infection and seroprevalence and anti-HEV and indication of previous exposure of different populations to HEV infection. Anti-HEV IgG assays vary in their performance and different studies have given widely different estimates of the seroprevalence of anti-HEV. Despite the establishment of an interim WHO International Reference Reagent (IRR, NIBSC code number 95/584) for antibodies to HEV in 1997, there are still wide discrepancies in the performance of anti-HEV assays. It was noted by the ECBS, at the time of establishment of the IRR that assays for anti-HEV were at an early stage of development and acknowledged that full assessment of new antibody assays requires panels of sera. Since the IRR was established, no international agreed unitage has been assigned to the preparation. In the original collaborative study, seven laboratories evaluated a range of mainly in-house developed assays and two commercial assays available at the time. Fifteen years later, diagnostic sensitivities and specificities as well as inter-assay agreement have been shown to vary widely for different kits for the detection of both anti-HEV IgM and IgG. Anti-HEV IgM is the major serological marker of acute or recent HEV infection; however, the main problem with detection of this marker is specificity; this is further compounded by a lack of sensitivity. Significant underestimations of seroprevalence of HEV (IgG) have been the result of lack of sensitivity of available assays. These assay issues, compounded by the failure of many clinical diagnostic laboratories to test for HEV infection as an alternative diagnosis of acute hepatitis, have impacted on the surveillance of incident hepatitis E and understanding the extent of asymptomatic infection.

Sally Baylis

Different collaborators will be involved in the collection and preliminary testing of NAT-confirmed cases of hepatitis E – with genotype confirmation, and subsequent collection of sera/plasma samples prior to formulation of the panel and evaluation in an international collaborative study alongside the IRR. It may be possible to assign an internationally agreed unitage to the IRR.

The proposal to prepare the anti-HEV panel was endorsed by the ECBS in October 2015.

### 2.2.3 Proposal for extension of WHO 1st Repository by Red Blood Cell Transfusion-Relevant Bacteria Strains, endorsed by ECBS in 2015

Description

Bacterial reference strains are a suitable tool for objective validation and assessment of various microbiological methods for blood safety and development of new techniques. Reference strains allow regulatory agencies, blood manufacturers, and companies who are developing novel screening methods and pathogen reduction technologies, to make informed decisions in a standardized manner. As a first milestone, four platelet transfusion-relevant bacterial strains were validated in an international study in cooperation with

the ISBT WP TTID Bacterial Subgroup (International Society of Blood Transfusion Working Party Transfusion-Transmitted Infectious Diseases). These bacterial strains were established in 2010 as the 1st WHO Repository of Platelet Transfusion-Relevant Bacterial Reference Strains (Störmer et al, 2014). After a second collaborative study in cooperation with the ISBT WP TTID Bacterial subgroup, 10 strains were added to the WHO Repository of Platelet Transfusion Relevant Bacterial Reference Strains in October 2015 for a total of 14 reference strains.

Statistically, the prevalence of bacterial contamination in RBC is 1 in 30,000 with septic reactions of 1 in 500,000 and projected fatality rates of approximately 1 in 10 million (Chen et al., 2008). Funk et al. (2011) reported four fatalities between 1997 and 2012 caused by transfusion of bacterially-contaminated RBC in Germany. The causative bacteria were *Staphylococcus aureus*, *Serratia marcescens* and *Yersinia enterocolitica*. From 2010 to 2014, US FDA reported one fatality caused by RBC contaminated with *Pseudomonas fluorescens*. Similarly, there was one case of a fatal transfusion reaction involving RBC contaminated with *Pseudomonas koreensis* documented in the Serious Hazards of Transfusion (SHOT) Report 2009. *Klebsiella pneumoniae* has also been implicated in a septic transfusion event involving contaminated RBC (Warnke 2013). Recently, Frati et al, (2015) published a case report of a RBC transfusion transmitted septic reaction with a fatal outcome in Italy caused by *Yersinia enterocolitica*.

Most bacteria isolated from platelet components, which are stored at room temperature, are unable to grow or even survive in RBC under mandatory cold storage conditions from 1°C to 6°C. Strains which are reported to proliferate to clinically significant levels in RBC are mainly psychrophilic bacteria, primarily gram-negative species such as *Serratia marcescens* and *Yersinia enterocolitica* (Ramirez-Arcos et al., 2013). Therefore, most of the WHO Repository of Platelet Transfusion Relevant Bacterial Reference Strains are not suitable as bacterial reference strains for RBC.

Eva Spindler-Raffel

In line with the strategy to establish relevant bacterial reference strains for all blood components and advanced therapy medicinal products (ATMPs), the next step will be to establish a bacterial panel for red blood cells (RBC).

The proposed list includes strains of the following transfusion of RBC relevant bacterial species:

Gram-positives: *Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus*, *Micrococcus luteus*, *Streptococcus pyogenes*, *Listeria monocytogenes*

Gram-negatives: *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Pseudomonas fluorescens*, *Pseudomonas aeruginosa*, *Yersinia enterocolitica*, *Serratia marcescens*, *Serratia liquefaciens*,

The proposal was presented to ECBS in October 2015, who endorsed it for future expansion to reference strains for RBC. Since November 2015, PEI has started to collect relevant candidate strains (isolates from RBC) worldwide. Cultivation, identification and pretesting in RBC are still ongoing to select appropriate strains for the collaborative study. Due to the fact that growth ability may vary among the bacteria species and even at the strain level, it is important to validate the candidate strains in an international collaborative study (cooperation with the ISBT WP TTID Bacterial subgroup).

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#### 2.2.4 Development of a WHO International Standard for Zika Virus RNA Nucleic Acid Amplification Techniques (NATs)

##### Description

On the 1st of February, 2016, Dr Margaret Chan, the director general of the WHO, declared a Public Health Emergency of International Concern due to the increase in neurological disorders and neonatal malformations seen in the Americas strongly suspected to be linked to the Zika virus (ZIKV) outbreak. This declaration came after a meeting of the International Health Regulations (2005) Emergency Committee. The WHO asked the PEI to develop a candidate international standard (IS) for ZIKV for nucleic acid amplification technique (NAT)-based assays. Such an IS or reference material will be used in diagnostic testing to ensure accurate diagnosis of ZIKV infection in the ongoing outbreak.

##### Sally Baylis

A candidate IS has been developed and consists of an inactivated, lyophilized ZIKV preparation formulated in a stabilizing, neutral solution and intended for dilution using a range of different types of sample matrix. The virus strain used for the preparation of the candidate IS originated from a ZIKV-infected patient from French Polynesia, closely related to ZIKV strains currently circulating in the Asia-Pacific region and central and South America. Further strains from the Asian ZIKV lineage were included in an international collaborative study as well as two preparations derived from African ZIKV isolates and the candidate international standard. The samples consisted of a mixture of inactivated ZIKV reference materials as well as clinical materials (urine or plasma) from ZIKV-infected patients. In addition, a panel of in vitro transcribed RNAs covering partial ZIKV genome sequences were included in the study. The aim of the collaborative study was to determine the potency of the candidate IS and related reference preparations using a range of NAT-based assays for ZIKV RNA and assign an internationally agreed unitage to the candidate WHO IS.

The samples for evaluation were distributed to 24 laboratories from 11 different countries. The samples were assayed on three separate days and the data were collated and analysed at the PEI. Data were returned by 21 of the participating laboratories, in total 37 sets of data were analysed; 19 from quantitative assays and 18 from qualitative assays. The assays used consisted of a mixture of in-house developed and commercial assays (currently available or in development). The results showed that all samples were detected consistently by the majority of participants. The candidate standard is very stable under recommended storage conditions, i.e. at or below -20°C, and is therefore suitable for long term use. On-going real-time and accelerated stability studies of the candidate IS are in progress. It is proposed that the heat-inactivated and lyophilized preparation with cell culture-derived French Polynesian ZIKV strain be established as the 1st IS for ZIKV RNA with an assigned unitage of 50,000,000 International Units per mL. This proposal will be reviewed at the WHO ECBS in October 2016.

#### 2.3 Membership in the Expert Advisory Panel on Health Laboratory Services

##### Heiner Scheiblauer

Dr Heiner Scheiblauer has been appointed by the WHO for a period of four years as a Member of the Expert Advisory Panel on Health Laboratory Services in November 2015. The mission of the Expert Advisory Panels and Committees (<http://apps.who.int/gb/bd/PDF/bd47/EN/regu-for-expert-en.pdf>) is "to contribute by correspondence technical information on developments in his or her field, and to offer advice as appropriate, spontaneously or upon request".

In practical terms, this is about supporting diagnostics and laboratory technology in developing countries,

notably to give guidance on the testing of HIV, HBV and HCV. The cooperation will mainly be with the WHO Prequalification Team (Essential Medicines and Health Products Department, WHO, Dr Gaby Vercauteren).

#### 2.4 Cooperation with WHO in the area of WHO's Prequalification Programme (PQ) for in vitro Diagnostic Devices (IVD) and Procurement of IVDs

PEI IVD Laboratory continued to participate in the WHO Programme for the Prequalification of Diagnostics (see [http://www.who.int/diagnostics\\_laboratory/evaluations/en/](http://www.who.int/diagnostics_laboratory/evaluations/en/)).

2.4.1 Review of product dossier submissions of IVDs for WHO Prequalification. Activities in the context of the cooperation with the WHO Prequalification Team of the Department of Essential Medicines and Health Products included product dossier reviews and on-site audits of various HIV, HBV and HCV IVDs. These evaluations by PEI-IVD and the Section of Molecular Virology support WHO in their prequalification of diagnostics for the access to safe, appropriate and affordable in vitro diagnostic devices of good quality in an equitable manner.

#### 2.4.2 Consultation on dossier and laboratory evaluation requirements for the emergency use assessment and listing (EUAL) procedure for Zika Virus in-vitro diagnostics, 14-15 March 2016

In February 2016 WHO opened the Emergency Use Assessment and Listing Procedure (EUAL) to candidate in vitro diagnostic devices (IVDs) intended for Zika virus diagnosis. The EUAL procedure serves to accelerate the availability of IVDs needed in public health emergency situations. It assists procurement agencies and Member States on the suitability for the use of a specific IVD. Dr Sigrid Nick and Dr Michael Chudy participated in the meeting for defining minimum WHO requirements for the acceptance of a dossier for the WHO EUAL of Zika antigen, antibody and NAT assays. Requirements for dossier and laboratory performance evaluations were finalized.

#### 2.4.3 Review of product dossier submissions of IVDs for WHO Emergency Use Assessment and Listing (EUAL) Procedure for Zika Virus Disease.

The WHO assists procurement agencies and Member States on assessing the suitability for use of Zika IVD based on a minimum set of available quality, safety, and performance data.

PEI supported the assessment of limited scope evaluations to verify critical analytical and clinical performance characteristics of Zika virus (Dr Sigrid Nick and Dr Heiner Scheiblauber for Zika virus IgM, Zika virus IgG and confirmatory tests; Dr Michael Chudy, Dr Julia Kreß and Dr Annette Reißinger for Zika virus NAT tests).

#### 2.4.4 Third Annual Meeting of WHO Prequalification of in vitro Diagnostics Dossier Assessors and Inspectors, 19-20 April 2016, Geneva

Dr Sigrid Nick and Dr Julia Kreß participated in the meeting which was held to discuss, improve and harmonize WHO's inspection and dossier assessment activities. Participants were informed and trained on the documents of the Technical Guidance Series (TGS1 Standards Applicable to WHO PQDx, TGS2 Establishing Stability and TGS3 Principles of Performance Studies).

#### 2.4.5 Participation in training activities of regulatory authorities and manufacturers linked to the PQ programme

2.4.5.1 Joint National Institute of Food and Drug Control (NIFDC) / WHO meeting on regulatory requirements of performance and stability studies for in-vitro diagnostic medical devices (IVD): Workshop on requirements for analytical and clinical performance and stability studies for in vitro diagnostic medical devices, Beijing, P.R. China 12-16 October 2015.

Dr Sigrid Nick served as a facilitator at this meeting. She also gave introductions into batch verification experience with HIV tests, requirements for performance evaluations (analytical) and the use and calibration of WHO International Standards. The topics discussed at the meeting were measures to ensure the quality of IVDs for HIV and hepatitis B and C.

2.4.5.2 Workshop for Indian manufacturers and the authority on regulatory requirements for performance and stability studies for in vitro diagnostic medical devices (IVD), 14-16 June 2016, New Delhi, India

Dr Sigrid Nick gave introductions into the batch verification experience with HIV tests, requirements for performance evaluations (analytical) and the use and calibration of WHO International standards. The topics

discussed at the meeting were measures to improve the quality of IVDs for HIV and hepatitis B and C dossiers for acceptance with the WHO PQDx.

## 2.5 International Nonproprietary Names (INN) of blood products and monoclonal antibodies

Description: Dr Karin Weisser of PEI has been working as Biological Advisor for the International Nonproprietary Names (INN, i.e. generic names) expert group since May 2006. 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 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 within the responsibility of the PEI.

In addition to the regular two consultations each year, separate WHO INN meetings on biological products have been held at intervals since 2002 to address general and specific aspects of nomenclature, including discussions on cell therapy products or biosimilars.

Karin Weißer

In April 2016, Dr Weisser became a full member of the INN expert group. She assessed 125 INN requests of biological and 56 INN requests of chemical substances from July 2015 to June 2016. She attended two consultations of the INN expert group (61st and 62nd consultation in October 2015 and April 2016) where all comments were discussed and decisions on the selection of INNs were taken.

## 2.6 WHO Meetings and Workshops (chronological order; HQ = Headquarters, Geneva, Switzerland)

### 2.6.1 Joint Assessment Meeting WHO Prequalification of in vitro Diagnostic Programme, WHO HQ, 5-9 October 2015

The meeting should enable participants to evaluate technical dossiers that are submitted for the approval of diagnostic tests. Participants were trained in groups and various sessions to evaluate e.g. performance evaluation studies, product stability and quality control. Part of the training was carried out by Dr Heiner Scheiblauer.

### 2.6.2 Workshop for development of a regional strategy for blood safety and establishment of a national regulatory system for blood and blood products, Cotonou, Benin, 22-25 September 2015

WHO/AFRO in collaboration with WHO/HQ convened a 3-day workshop in Cotonou, Benin, from 23 to 25 September 2015 to address the challenges of the blood and blood products situation in the WHO African Region, to update the regional strategy for blood safety and to establish a regulatory system, which are crucial for the improvement of the availability, affordability and use of safe, effective and quality assured blood and blood products in the African Region. Dr Jens Reinhardt participated in the workshop and gave a talk on "Blood products regulatory aspects: experiences from Germany".

### 2.6.3 WHO International consultation on regulatory systems strengthening, WHO HQ, 2-3 December.

Dr Jens Reinhardt participated in the "2nd WHO International Consultation on Regulatory Systems Strengthening" which took place at WHO headquarters, Geneva from 2-4 December 2015. The scope of the meeting was the update on the development of the WHO Global Assessment Tool.

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

### 2.7.1 IPFA/PEI (International Plasma Fractionation Association) 23rd International Workshop on Surveillance and Screening of Blood Borne Pathogens, Lisbon, Portugal, 25-26 May 2016

PEI co-organizes this annual scientific meeting. The primary focus concerns the application of nucleic acid amplification tests (NAT) and other measures to increase blood safety, with standardization of assays being one of the regular topics in this series of meetings. Dr Johannes Blümel, Dr Michael Chudy, Dr Julia Kress, Dr Heiner Scheiblauer and Dr Astrid Schwantes attended the meeting in May 2016.

The well attended workshop – more than 200 participants mainly from blood banks, academic institutions, regulatory authorities and diagnostic industry – focused on the phylogeny of established blood borne viruses,

arbovirus transfusion transmission (ZIKV epidemic), understanding of the residual viral transmission risk (presentation of the draft WHO guideline by Dr Michael Chudy), screening strategies for HBV, updates on HEV, MSM policy changes as well as alternative blood safety strategies and the impact of pathogen reduction. Progress in the development of blood screening IVDs was presented in the manufacturers' session which included the current update on screening NAT tests for Zika virus.

2.7.2 SoGAT (Standardization of Gene Amplification Techniques) – 4th Joint Blood Virology and Clinical Diagnostics Meeting/ SoGAT Workshop, London, UK, 6-8 June 2016

The third joint meeting of the two SoGAT groups (blood virology, clinical diagnostics) was attended by Dr Michael Chudy and Dr Annette Reissinger. In the second session chaired by Dr Jacqueline Fryer, NIBSC and Dr Michael Chudy the participants discussed the final draft of the WHO Manual on Calibration of Secondary Standards (prepared by a group around Michael Chudy, PEI).

2.8 Further conferences with CC relevant topics attended by PEI co-workers (chronological order)  
International Society of Blood Transfusion (ISBT); Working Party-Transfusion Transmitted Infectious Diseases, London, UK, 27 June - 1 July 2015.

Presentations by Dr Spindler-Raffel: "Enlargement of WHO Repository PC Transfusion-Relevant Bacteria Reference Strains" and "Growth kinetics of different bacteria species at low storage temperature – Relevance for Red Blood Cells".

48th Annual Assembly of the German Society for Transfusion Medicine and Immunohematology (DGTI), 15 September 2015, Basel (Switzerland).

Professor Seitz gave a presentation entitled "What qualifies Haematopoietic Stem Cells as ATMP?" as a contribution to a satellite symposium organized by Swissmedic on the topic: "Regulatory aspects in transfusion medicine and current challenges".

European Symposium: IV Wildbad Kreuth Initiative - Optimal use of clotting factors and platelets, 6-7 May 2016, Freising, Germany.

The PEI was co-sponsor of this conference, together with the EDQM and the Ludwig-Maximilians-University Munich. Professor Seitz, Dr Anneliese Hilger and Dr Dorothea Stahl were members of the Scientific Programme Committee, moderators and rapporteurs of sessions, and contributed the following presentations: "Continuing the Kreuth Initiative: Current controversies in clinical use of blood components" (Professor Seitz), "Clinical trials of clotting factors/regulatory aspects" (Dr Hilger), and "Availability of platelet concentrates in Europe" (Dr Stahl).

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

3.1 5th Meeting of WHO Collaborating Centres (CC) to support the development of WHO Biological Reference Preparations for in vitro Diagnostic Devices, NIBSC, Potters Bar, UK, 2-3 July 2015

The meeting was performed to coordinate needs of WHO programmes, to discuss priority projects in order to avoid an overlap of activities and to strengthen the collaboration within the WHO CC Network, but also to agree on proposals to be put forward to ECBS for endorsement or establishment. Thus the meeting comprised scientific updates on ongoing projects, an update on WHO Guidance Documents, general discussions on important topics and the proposals to ECBS.

The PEI participated in the meeting with five scientists on site (Dr Kress, Dr Nick, Dr Spindler-Raffel, Dr Unger, and Dr Reinhardt) and five scientists via teleconference (Professor Seitz, Dr Chudy, Dr Baylis, Dr Knauer, and Dr. Reissinger). Jens Reinhardt from PEI shared the rapporteurship for the blood/IVD track with Clare Morris (NIBSC).

3.2 WebEx Meetings of WHO Collaborating Centres to support the development of WHO Biological Reference Preparations for Blood Products and in vitro Diagnostic Devices

Physical meetings of the WHO CC Network are scheduled for every other year (see 3.1). In between, WebEx meetings are performed for discussions on the activities described in point 3.1.

3.2.1 1st WebEx Meeting of WHO Collaborating Centres to support the development of WHO Biological Reference Preparations for Blood Products and in vitro Diagnostic Devices, 31 March 2016

Participants of PEI: Dr Michael Chudy, Dr Julia Kreß, Dr Annette Reissinger, Dr Sally Baylis, Dr Heinrich Scheiblauber, Nina Wissel, Dr Gerrit Praefcke, Dr Dorothea Stahl, Dr Johannes Dodt, Professor Rainer Seitz, Dr Gabriele Unger.

3.2.2 2nd WebEx Meeting of WHO Collaborating Centres to support the development of WHO Biological Reference Preparations for Blood Products and in vitro Diagnostic Devices, 21 June 2016

Participants of PEI: Dr Julia Kreß, Dr Annette Reissinger, Dr Sally Baylis, Dr Heinrich Scheiblauber, Nina Wissel, Dr Gerrit Praefcke, Dr Dorothea Stahl, Professor Rainer Seitz, Dr Eva Spindler-Raffel.

3.3 Participation in collaborative studies of WHO International Blood Product Standards

In 2015, the PEI section 7/3 "Batch Release of Blood Products, Logistics", Division "Haematology" participated in the collaborative study to value assign potencies to the replacement International Standards for Factor XI, plasma (CS546). The report was distributed to participants for comments and agreement in March 2016. The report was submitted to the SSC meeting of the International Society on Thrombosis and Haemostasis (ISTH) in May 2016 with the aim of establishment by the ECBS in October 2016.

Section 7/3 also took part in a collaborative study to assess the comparability of new FVIII products with the WHO International Standards (CS540). According to the organizer of the study (NIBSC) the data from all of the labs have been analysed and the report will be written over the summer with an expected completion by early autumn this year.

Furthermore, two sections in the Division "Haematology" (Section 7/3 and research group 7/01) have agreed to participate in the collaborative study to assign potency to the 2nd International Standard for Factor IXa. Sample shipment for this study is scheduled for July 2016.

3.4 Participation in collaborative studies for the establishment or replacement of WHO International Standards for NAT based assays for blood borne viruses

In the reporting period, the Section Molecular Virology, Division Virology at PEI, participated in the following WHO collaborative study:

- Proposed 4th WHO International Standard for Hepatitis B Virus for NAT-based assays (NIBSC, Potters Bar, UK).

**4. Please briefly describe any type of technical, programmatic, advisory or other support received from WHO during the past 12 months for the implementation of the agreed activities listed above (if any).**

n/a



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