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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 07-2017 to 07-2018

1. Annual report on the agreed workplan

Describe progress made on the agreed workplan. For each activity, detail (1) the actions taken, (2) the outputs delivered, as well as (3) any difficulties that may have been encountered. Three responses are expected. [maximum 200 words per activity]. Indicate, if an activity has been completed previously, has not yet started or has been placed on hold.

Activity 1

Title: Development of an International Anti-Hepatitis E Reference 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.

The importance of reference materials for the diagnosis of HEV infections was discussed at the WHO Expert Committee for Biological Standardization which asked for and also endorsed this important project.

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.

Different collaborators are already 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.

Status: ongoing

The proposal to prepare the anti-HEV panel was endorsed by the ECBS in October 2015. Plasma has been obtained from recovered patients and donors with further units being screened. The period of sample collection/identification has been completed and materials are undergoing characterization prior to further processing and evaluation in a collaborative study.

The activity is led by Dr Sally Baylis.

Activity 2

Title: Development of the 1st International Chikungunya virus reference reagent for serology

Description: The mosquito-borne Chikungunya virus (CHIKV) is a member of the Alphavirus genus in the Togaviridae family. Chikungunya was first identified in Tanzania in the early 1950s. The disease occurs not only in Africa but also in Asia and the Indian subcontinent and, since 2013, has spread to the Americas, particularly central and Southern areas. Small outbreaks have also occurred recently in Europe.

The diagnosis of Chikungunya requires a variety of tests including detection of IgM and IgG antibodies. Co-circulation of Chikungunya virus with Dengue virus (DENV) and Zika virus (ZIKV) frequently occurs and infections cause by these viruses share common signs and symptoms in infected patients. Accurate diagnosis and discrimination of CHIKV from other virus infections is important for patient care. Analysis of IgM antibodies is particularly useful for the confirmation of acute infection. Anti-CHIKV IgG may also be detectable during acute infection. Anti-CHIKV IgG is also a marker of past CHIKV infection and seroprevalence and anti-CHIKV and indication previous exposure of different populations to CHIKV infection.

Anti-CHIK assays vary in their performance (for example, Niedrig et al. Clin Microbiol Infect. 2009;15:880 and Prat et al. Emerg Infect Dis. 2014;20:2129).

Status: ongoing

The proposal to establish a reference reagent was endorsed by the WHO ECBS in October 2016. Plasma has been collected from blood donors as well as recovered patients and the lead candidate material was evaluated in an external quality assurance study coordinated by INSTAND involving 39 participating laboratories using a variety of different methods, the candidate material was well detected by all participants. The materials for the WHO collaborative study are scheduled to be lyophilized in Q4 2018 and the collaborative study is expected to commence early in 2019.

The activity is led by Dr Sally Baylis.

Activity 3

Title: Development of the 1st International Standard for Chikungunya Virus (CHIKV) RNA for NAT-based

Description: Chikungunya virus is a blood borne pathogen transmissible by mosquitoes that has the potential to be transmitted by blood transfusion. The availability of an international standard for Chikungunya virus RNA would facilitate the development and quality control of new NAT assays for use in blood donor screening and in medical diagnostic testing. Such assays would significantly improve the safety of the blood supply worldwide. The topic was assigned high priority by the ECBS, and WHO was requested to provide these materials as soon as possible.

The International Standard for Chikungunya virus RNA will be used as a global standard for the development of assays for the detection of Chikungunya infections in blood donors. It may also be used as a reference standard to evaluate the performance of assays for detection of Chikungunya viral RNA. Users will be blood donor screening and diagnostic test developers, blood banks, hospitals, clinical laboratories and other establishments performing Chikungunya testing.

Status: ongoing

A proposal for the establishment of an International Standard (IS) for CHIKV RNA for NAT-based assays presented by the Center for Biologics Evaluation and Research (CBER) of the U.S. Food and Drug Administration (FDA) was endorsed by WHO ECBS in October 2010. CBER established a well-characterized (national) CHIKV RNA reference reagent (Añez G et al., Genome Announc, 2014; Añez G et al., Vox Sang., 2015) and suggested to use the same vial stock for the development of the candidate IS. The project was transferred from CBER to PEI in March 2016.

The candidate IS was prepared using CHIKV isolate R91064 (East/Central/South African genotype/Indian Ocean lineage, GenBank accession no. KJ941050), imported from India to the US in 2016. The virus stock was propagated in Vero cell culture, heat-inactivated, diluted in negative human plasma and lyophilized.

An international collaborative study was conducted to assess the suitability of the candidate IS for use in NAT assays. Further clinical materials from CHIKV infected patients from Brazil and Mauritius were included in the study to evaluate commutability. A total of 25 laboratories from 14 countries agreed to participate in the study. Twenty-four laboratories returned 31 datasets (11 quantitative and 20 qualitative) from 17 commercial assays. Statistical analysis of data was performed to evaluate the potencies of the candidate IS and the clinical samples. Potencies were determined by end-point dilution and probit analysis (qualitative assays) and calculation of mean estimates (quantitative assays). Reduction in assay variability and harmonization of data was observed for all study samples when results were expressed relative to the candidate IS, which demonstrated the need for standardization.

The candidate IS was established by WHO ECBS in October 2017 as the 1st IS for CHIKV RNA for NAT-based assays with an assigned unitage of 2,500,000 International Units (IU)/mL. Stability studies are ongoing and indicate that the preparation is stable and suitable for long-term use.

The activity is led by Dr Julia Kress.

Activity 4

Title: Development of the 1st International anti-HCMV IgG Standard

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. WHO Expert Committee for Biological Standardization discussed the need for an international Standard expressed in IU/ml and endorsed the project.

In 2012 samples were sourced by PEI and tested for suitability for a possible candidate material as well as possible accompanying study samples selected. In April 2013 the project was shown to the WHO Collaborating Centre's meeting and the proposal provided to the ECBS was adopted in October 2013. A Collaborative Study was carried out between 2014 and 2016 to establish the candidate standard. Overall, a candidate anti-CMV IgG standard was developed with an assigned unitage of 46.4 units per mL and vial. In view of the variety of the anti-CMV tests, and their currently non-comparative performance, it is expected that the candidate standard will significantly facilitate comparability between the tests and make the results more reliable.

Status: ongoing

The 1st WHO International Standard for CMV IgG antibodies was adopted by the ECBS in October 2017. CMV infection is a major cause of disease and death in immunosuppressed patients, including those receiving organ transplants, and the world's leading viral cause of birth defects. Control of CMV infection and reduction of CMV transmission through blood and tissue preparations are therefore in the public health interest, including the question of the best diagnostic methods. One of the most important tests for diagnosis of CMV infection are CMV antibody tests for immunoglobulin class IgG (anti-CMV IgG). However, current CMV IgG antibody tests suffer from the fact that their results are so different that they are not comparable. The new standard now provides the ability to standardize the calibration of anti-CMV IgG test kits to unify the output of the result. It can also be used for quality control and to determine the analytical sensitivity of anti-CMV IgG test kits. The suitability of the international standard was determined in a WHO collaborative study organized by the Paul Ehrlich Institut (PEI). Sixteen laboratories from 9 different countries have tested the standard with a variety of 16 anti-CMV tests in different formats. The results show that calibration of anti-CMV IgG test kits with the standard considerably facilitates comparability of the tests making interpretation of the results safer. The first international WHO standard for anti-CMV IgG for serological assays is now available from PEI (code 136616/17), with 46.4 international units per mL assigned. The activity is led by Nina Wissel and Dr Heinrich Scheiblaue.

Activity 5

Title: Extension of the WHO repository for Transfusion Relevant Bacteria Strains - Validation study for Red Blood Cell Relevant Reference Strains

Description: Bacterial contamination of blood components is one of the major threats in transfusion medicine. WHO has been approached by international organisations in the blood field to improve the situation of contamination testing by provision of international reference materials. The WHO Expert Committee for Biological Standardization discussed this issue and endorsed the project of bacteria repository and its expansion.

As a first milestone four Platelet Transfusion Relevant Bacteria Strains were validated in an international study and established in 2010 as the 1st WHO Repository of Platelet Transfusion Relevant Bacterial Reference Strains. The proposal to enlarge the repository was also endorsed by WHO ECBS in 2010. The report of the collaborative study was sent to WHO ECBS for endorsement/adoption at the ECBS Meeting in Geneva in October 2015.

In line with the strategy to establish Relevant Bacterial Reference Strains for all blood components and 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 relevant bacterial species:

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

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

Status: ongoing

Bacterial strains, mainly isolates from transfusion incidents involving Red Blood Cell (RBC) concentrates, were collected and characterized for their growth properties in RBC. Bacterial suspensions of suitable candidate strains were manufactured and the stability upon storage at -80°C was evaluated. In a next step, frozen vials of the strains *Listeria monocytogenes* PEI-A-199, *Serratia marcescens* PEI-B-P-56, *Serratia liquefaciens* PEI-A-184, *Pseudomonas fluorescens* PEI-B-P-77, *Yersinia enterocolitica* PEI-A-105, *Yersinia enterocolitica* PEI-A-176 were shipped to 18 laboratories worldwide. The cooperation partners currently perform or already completed the artificial contamination of red blood cells units. The testing includes the spiking of RBC with a low concentration of bacterial cells and samples are taken to determine the number of colony forming units over time. Preliminary results were presented at the Transfusion Transmitted Infectious Diseases WP meeting (ISBT Toronto), June 2018. The finalization of the laboratory procedure is expected to be in fall 2018. Based on a statistical analysis, a bacterial reference panel for RBC composed of strains showing robust and reliable growth in RBC will be established.

The activity is led by Dr Oleg Krut and Dr Marcel Prax.

Activity 6

Title: Participation in the Blood Regulators Network (BRN)

Description: WHO recognized the need for rapid and reliable external advice in the field of blood and blood safety. 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. Current topics are support to continuous implementation of Resolution WHA63.12 and the BRN document "Assessment Criteria for National Blood Regulatory Systems"; ongoing revision of the existing WHO NRA (national regulatory agency) assessment tools to include the WHO assessment criteria for blood regulatory systems; BRN supports requests for assessment of blood regulatory systems, e.g. in the African region (ICDRA 2017 recommendation); evaluation of new developments such as pathogen inactivation technology for blood components, storage of red blood cells; discussion of opportunities for international convergence of regulations; proposed guidelines on recombinant DNA derived biotherapeutics; results of EBoV (Ebola Virus) clinical trials using convalescent plasma performed in Guinea; and discussions on national decision making on the MSM deferral (e.g. US FDA, impact of ART).

Status: ongoing

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 related to blood and blood regulation aspects to WHO.

Current topics are:

Support to continuous implementation of Resolution WHA63.12 and BRN document "Assessment Criteria for National Blood Regulatory Systems"; ongoing revision of the existing WHO NRA (national regulatory agency) assessment tools to include the WHO assessment criteria for blood regulatory systems; validation of the WHO Global Benchmarking tool with integrated BRN criteria in selected African states; BRN supports requests for assessment of blood regulatory systems, e.g. in the African region (ICDRA 2016 recommendation); evaluation of the storage of red blood cells; discussion of opportunities for international convergence of regulations; and is currently drafting a position paper on HEV and possible implication on regulation of blood components for transfusion.

Dr Anneliese Hilger is chair of the BRN.

Activity 7

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

Description: WHO undertakes the project to enable LMICs to make use of blood components currently discarded as biological waste. "Improving access to medical products through local production and technology transfer" should increase access, especially for the poor in developing and least developed countries to medicines, vaccines and diagnostics of importance to public health, and especially for neglected diseases of the type II and type III categories as well as the specific needs of developing countries in relation to type I diseases.

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. 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/inspectors will contribute by facilitating meetings and training courses in several regions of the world.

Status: ongoing

Regional Workshop on the Regulatory System for Blood and Blood Products, Douala, Cameroon, 21-23 March 2018

This workshop focused on the need for national blood regulatory systems as a requirement for the provision of safe and efficacious blood products. Key elements of blood regulation include oversight of quality systems and assurance of technical standards with independent decision-making of the national regulatory system in the context of a nationally coordinated blood system. Dr M Nübling, Dr V Klümpers and W Samukange from PEI participated in this workshop as facilitators, giving presentations on the experience with previous assessments of blood regulation in African countries and on the Global Health Protection Program (GHPP) of PEI performed in the blood field. As a result of the workshop the future establishment of a Forum of Blood Regulators in Africa was decided in order to facilitate sustainable capacity development in the interest of regulatory harmonization, information exchange, and mutual support for implementation of effective regulation of blood and blood components.

WHO Multi Criteria Decision Analysis (MCDA) Risk Decision Support Tool Consultation, Arusha, United Republic of Tanzania, 18 June 2018

This workshop goes back to the 2017 efforts of WHO HQ to provide to blood regulators and blood operators a software tool for the estimation of the impact of emerging infections onto the national blood supply. Such a tool would ensure consistency between different estimations and the results would allow consistent decision making in a national blood system. In this workshop input was sought from African stakeholders. Dr CM Nübling and W Samukange from PEI participated in this workshop, sharing their experience with decision making based on risk estimations in Europe.

2. Annual report on other activities requested

Should WHO have requested activities in addition to the agreed workplan, please describe related actions taken by your institution [maximum 200 words]. Please do not include in this report any activity done by your institution that was not requested by and agreed with WHO.

2.1 67th Meeting of the Expert Committee on Biological Standardization (ECBS), Geneva, Switzerland, 17-20 October 2017

The president of the PEI, Professor Cichutek, acted as chairman of the ECBS.

At the ECBS an update on the ongoing main activities of the PEI WHO Collaborating Centre (CC) was presented.

The results of the CMV IgG standard were presented by Dr Heiner Scheiblauber and put up for discussion. As a result, the 1st International Standard for Cytomegalovirus (CMV) IgG antibodies was adopted. In addition, further standardization projects in accordance with the ECBS agenda were discussed.

Another standardization project at the PEI, the 1st WHO International Standard for Chikungunya virus (CHIKV) RNA for nucleic acid amplification technique (NAT)-based assays, was presented for endorsement by the committee by Dr Julia Kress. At the end of this ECBS meeting, the committee adopted the 1st WHO International Standard for CHIKV RNA for NAT-based assays.

Dr Jens Reinhardt (PEI) shared the rapporteurship for the blood/IVD track with Dr Clare Morris (National Institute for Biological Standards and Control, NIBSC). The entire activities of the ECBS are laid down in the report which will be published in 2018 in the WHO Technical Report Series (TRS).

2.2 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.

2.2.1 Review of product dossier submissions of IVDs for WHO Prequalification

Activities in collaboration with the WHO prequalification team in the Essential Medicines and Health Products department have now become routine. PEI-IVD and Section Molecular Virology are regularly asked to review product dossiers. The focus is on rapid tests for the diagnosis of HIV, HBV and HCV. In the past year, 1 HBsAg rapid test and several HIV rapid tests were evaluated. These evaluations of PEI-IVD and the Molecular Virology Section support WHO in the prequalification of diagnostics for access to safe, appropriate and affordable good quality in vitro diagnostics in a fair manner.

2.2.2 4th Annual Meeting of WHO Prequalification of In Vitro Diagnostics Dossier Assessors and Inspectors, WHO HQ, 25-27 April 2017

Dr Heiner Scheiblaue participated in the meeting. An overview was given of the review of the WHO PQDx dossiers in 2016-2017 and the opportunities/challenges for the coming year. Points that were discussed among others included:

- Data Integrity - Handling unexpected data.
- Role of technical experts in inspections
- New Technical Specification Series (TSS) and Technical Guideline (TGS)
- TSS-1 HIV RDTs for professional use and/or self-testing
- Introduction to the classification tool for dossier evaluation
- Good reporting for dossier assessors.

These activities expand the WHO's assessment of tests used in less developed countries around the world and also expand the scope for the PEI.

2.2.3 Regulatory requirements for assessment of in vitro diagnostic medical devices (IVD), National Institute of Biologicals (NIB), Noida, India, 8-12 August 2017

A WHO training was organized by the WHO Essential Medicines and Health Products Department, RSS Team for IVD experts from the NIB and inspectors from the CDSCO (Central Drugs Standard Control Organization) in India. Dr Sigrid Nick served as a facilitator in the meeting. Topics dealt with by S Nick were the understanding of regulatory approvals (contents of EU certificates), review of product design, analytical performance studies, sensitivity, specificity, precision and robustness as well as stability studies, lot release testing and good regulatory practice including experience from the European Union and changes with the new IVD regulation.

2.2.4 Joint WHO/ PEI Training Programme of Indian experts at the Testing Laboratory for IVD Medical Devices at the Paul Ehrlich Institute (PEI-IVD), Langen, Germany, 11-15 December 2017

The training was carried out on behalf of WHO Essential Medicines and Health Products Department, RSS Team. Training was given by Sigrid Nick, Olivia Knauer, Heiner Scheiblaue. The purpose of this training for the Indian experts was to carry out a batch release test for HIV rapid tests, covering both specific technical aspects and the subordinate processes and procedures concerning organisation of the laboratory. Specific technical topics of the training included: principles of batch testing and performance evaluation, establishing test criteria, establishing suitable samples and panels, panel production, maintaining continuity of values, testing algorithms for dealing with OOS results and decision taking, laboratory organization, record and data storage and quality management.

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

From July 2017 to June 2018, Dr Karin Weisser assessed 134 INN requests of biological and 107 INN requests of chemical substances. She attended two consultations of the INN expert group (65th and 66th consultation, October 2017 and May 2018, resp.) where new and outstanding applications were discussed and decisions on the selection of INNs were taken. At the 66th consultation in May 2018 she was elected by the group to act as vice chair for Biologicals.

2.4 WHO Meetings and Workshops

WHO meeting on Tuberculosis IVDs Standardization, WHO Headquarters, Geneva, Switzerland, 24 January 2018

The meeting was organized to get consensus among stakeholders on standardization efforts for TB diagnostics. A project on standardization of TB NAT assays was discussed in more detail, NIBSC will take the lead in this project, in cooperation with other partners like FIND or PEI. Dr Oleg Krut attended the meeting.

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

2.5.1 SoGATS/SID (Standardization of Genomic Amplification Techniques and Serology/ Standardisation of Infection Diagnostics) – London, United Kingdom, 11-12 June 2018

Dr M Chudy, Dr A Reissinger, K-M Hanschmann and Dr M Nübling represented PEI in this international standardisation meeting. K-M Hanschman presented how International Units are derived for the establishment of First International Standards, M Chudy contributed his experience with the WHO International Standard for HDV RNA in the commutability session, M Nübling co-chaired the session on evaluation of new reference materials.

2.6 Further conferences with CC relevant topics attended by PEI co-workers (chronological order)
Biennial Meeting of the Joint Committee for Traceability in Laboratory Medicine (JCTLM) – Bureau International des Poids et Mesures, Sèvres, France, 4-5 Dec 2017

Dr Gabriele Unger attended the biennial members' and stakeholders' meeting, where Dr Almond, National Institute for Biological Standards and Control (NIBSC) gave an overview of SOGAT activities (see above), including WHO International Reference Preparations developed by PEI.

Workshop on Chikungunya vaccines - challenges, opportunities and possibilities, New Delhi, India, 5-6 Feb 2018

Dr Sally Baylis and Professor Barbara Schnierle attended the meeting. Dr Baylis was involved in the panel discussion: concerning biological standards, assays and animal models.

Workshop on Human platelet lysate – current standards and future development, International Society of Blood Transfusion, Zurich, Switzerland, 22-23 March 2018

Dr Johannes Blümel and Dr Astrid Schwantes attended the meeting and Dr Schwantes gave a talk on the virus safety expectations of platelet lysates.

IPFA/PEI 25th International Workshop on “Surveillance and Screening of Blood-borne Pathogens”, Athens, Greece, 16-17 May 2018

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. With nearly 200 participants mainly from blood banks, academic institutions, regulatory authorities and diagnostic industry the workshop 2018 was again well-attended; the opening was by Dr K Cichutek, president of PEI, who also co-chaired the session on new technologies. The Paul-Ehrlich-Institut commitment to the workshop was renewed. Dr M Nübling gave a presentation on T Evers, former head of IPFA and initiator of the workshop series; Dr Nübling also chaired the session on risk-modelling. Further PEI representatives were Dr J Kress and Dr M Chudy who chaired the update session and who had been involved the conference preparation.

International Society of Blood Transfusion (ISBT); Working Party-Transfusion Transmitted Infectious Diseases, Toronto, Canada, 2-6 June 2018

Dr Marcel Prax and Dr Oleg Krut attended the meeting and Dr Prax gave a talk on: “Update on the ISBT TTID study on establishment of bacterial reference strains for RBC”.

3. Resources

Indicate staff time spent on the implementation of activities agreed with WHO (i.e. those mentioned in questions no. 1 and no. 2 above). Do not include any data related to other activities done by your institution without the agreement of WHO. Please indicate staff time using the number of “full-day equivalents” – a day of work comprising 8 hours (e.g. 4 hours work per day for 7 days should be recorded as 3.5 full-day equivalents).

Number of staff involved (either partially or fully)

Senior staff	Mid-career staff	Junior staff, PhD students
17	13	0

Number of full-day equivalents, total for all staff involved

Senior staff	Mid-career staff	Junior staff, PhD students
225	280	0

Implementation of the agreed workplan activities (i.e. those mentioned in questions no. 1 and no. 2 above) normally require resources beyond staff-time, such as the use of laboratory facilities, purchasing of materials, travel, etc. Please estimate the costs of these other resources as a percentage of the total costs incurred (e.g. if you incurred costs of USD 100 and the value of your staff time was USD 50 which makes the total of USD 150, please report 33.3% and 66.7%).

Percentage of costs associated with staff time	Percentage of costs associated with other resources	Total
75.00	25.00	100.00

4. Networking

Describe any interactions or collaboration with other WHO Collaborating Centres in the context of the implementation of the agreed activities If you are part of a network of WHO Collaborating Centres, please also mention the name of the network and describe your involvement in that network [maximum 200 words].

4.1 (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. In between, WebEx meetings are performed for discussions on the ongoing activities.

4.1.1 4th WebEx Meeting of WHO Collaborating Centres to support the development of WHO Biological Reference Preparations for Blood Products and in vitro Diagnostic Devices, 6 July 2017

Participants of PEI: Dr Julia Kress, Dr Annette Reißinger, Dr Heiner Scheiblauer, Dr Gabriele Unger, Nina Wissel, Dr Jens Reinhardt (rapporteur)

Presentation by Dr J Kress: "Update on the Development of the 1st WHO IS for Chikungunya Virus RNA for NAT-based Assays".

Presentation by Dr H Scheiblauer: Establishment of the 1st IS for anti-CMV IgG.

4.1.2 5th WebEx Meeting of WHO Collaborating Centres to support the development of WHO Biological Reference Preparations for Blood Products and in vitro Diagnostic Devices, 20 July 2017

Participants of PEI: Dr Michael Chudy, Dr Julia Kress, Dr Dorothea Stahl, Dr Winfried Kammer, Dr Gabriele Unger, Dr Anneliese Hilger, Dr Johannes Dodt, Dr Susanne Breitner-Ruddock, Dr Marcel Prax, Dr Sabine Wegehaupt, Dr Annette Reissinger.

Dorothea Stahl (PEI) presented an outline prepared by the Section Transfusion Medicine of PEI (Winfried Kammer, Dorothea Stahl) on the need to develop reference material requirements to support the quality of blood components as well as whole blood derived from blood donors and also from patients:

Blood components and whole blood are considered to be essential medicines according to resolution WHA 63.12 and as indicated by the WHO Model List of Essential Medicines. Regulation of blood components and whole blood as essential medicines requires characterization of drug substance (i.e. amount, concentration) as well as of impurities. Currently no biological reference materials are established as a reference source of defined biological activity expressed in an internationally agreed unit to standardize the measurement of drug substances and of impurities in blood components (RBC concentrates, PLT concentrates, FFP) and in whole blood units. In addition, patient blood samples are analyzed for haemoglobin content in various clinical settings using various methodological approaches. These techniques are not standardized using international reference preparations that are independent of the quality control materials supplied by manufacturers of test systems.

Taking RBC concentrates and whole blood units as an example, a draft proposal was discussed to establish a reference preparation of defined biological activity to standardize the characterization of the drug substance in cellular products. As reference preparation intact frozen erythrocytes are considered.

Anticipated worldwide uses // users are (1) quality control of RBC concentrates and whole blood (product quality) // blood establishments, blood banks, medical device manufacturers, OMCL, (2) characterization of

donor blood in the context of the donation process (donor safety) // blood establishments, medical device manufacturers, OMCL, and (3) characterization of patient blood in the context of transfusion decision (Patient Blood Management) or other clinical decisions // blood banks, clinical laboratories, clinical laboratories control authorities, medical device manufacturers.

It was mentioned that there are already three WHO standards for haemoglobin but these are related to disease diagnosis, and consist of haemoglobin instead of intact erythrocytes (Haemoglobin A2, Beta-thalassemia haemolysate derived, lyophilized // Haemoglobin F, Cyanmethaemoglobin, haemolysate derived, lyophilized // Haemoglobincyanide, from bovine haemoglobin, liquid). Another contribution was that it is unclear how the use of the standard will be and whether it will be taken up by testing laboratories. Tests have been in place for several decades. Where is the driver for this reference preparation? The response was that there are many different methods for haemoglobin measurement and only commercial standards are used. There is a real need for harmonization of testing haemoglobin in whole blood samples. This standard could be applied to non-invasive measurement where reliance on current methods and technology is limited. It was concluded that there are two prerequisites for this project: to demonstrate the need for the new reference and to show it will be effective for harmonization; a pilot study to show commutability with and harmonization between different assays using samples from different donors could be convincing. There was also the question how the material will be value assigned; it was proposed to use HPLC for its characterization, an approach different from a consensus value obtained by all methods. Further remarks were in regard to potential impact of frozen red cells on haemoglobin measurement, and the need to have a dialogue with haemoglobin test manufacturers. Also a survey may be performed prior to present this project for endorsement at ECBS. Discussion points will be taken into consideration to further proceed with this project.

4.1.3 6th Meeting of WHO Collaborating Centres to support the development of WHO Biological Reference Preparations for Blood Products and in vitro Diagnostic Devices, 10-12 April 2018, Silver Spring, U.S.A. CBER/FDA hosted the 6th Meeting of the Collaborating Centres. Dr Julia Kress and Washington Samukange participated in the meeting on the FDA campus.

PEI Participants via WebEx: Dr Sally Baylis, Dr Johannes Dodt, Dr Winfried Kammer, Dr Oleg Krut, Dr Micha Nübling, Dr Manvi Porwal, Dr Gerrit Praefcke, Dr Marcel Prax, Dr Annette Reissing, Dr Barbara Schnierle, Dr Dorothea Stahl, Dr Gabriele Unger.

Sally Baylis participated in the meeting via WebEx and presented updates on chikungunya virus and hepatitis E virus projects. Marcel Prax gave a presentation on the "Expansion of bacterial reference panels".

4.2 Participation in WHO collaborative studies for blood products

In 2017, the PEI section 7/3 "Batch Release of Blood Products, Logistics", Division "Haematology" participated in the collaborative studies to assign potency to the 2nd International Standard for Factor IXa, the 2nd International Standard for Factor V, plasma (16/374) and the 3rd International Standard for Prekallikreinactivator.

4.3 Participation in WHO collaborative studies for IVD

The Virus Safety section at PEI participated in the collaborative study to establish the 1st WHO International Standard for antibodies to Zika virus. The study was organized by NIBSC, UK.

Section Molecular Virology at PEI participated in the collaborative study to establish the 2nd WHO International Standard for HIV-2 for NAT-based assays. The study was organized by NIBSC, UK.