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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

07-2022 to 07-2023

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 and/or participation in collaborative studies under WHO's leadership, to support WHO in the development of International WHO Reference Preparations (IRP)

Description: The development, establishment and promotion of international (biological) reference preparations (IRP) is a core function of WHO, set out in its Constitution (Article 2).

WHO's normative work has again been emphasized in the "Thirteenth General Programme of Work 2019–2023" (GPW13): "What is new in GPW 13?". WHO will strengthen its normative work. Setting norms and standards is a unique function and strength of WHO; it underpins the special position that WHO enjoys in global health, in which the Organization, through the Health Assembly, has the "authority to adopt conventions or agreements with respect to any matter within the competence of the Organization" as well as regulations and recommendations. The WHO Secretariat will reinforce its science- and evidence-based normative work, anticipate and assess the impact of research and discovery on public health and focus on supporting countries in the implementation of WHO's norms, standards and agreements." This activity contributes to the GPW 13 outcome 1.3, improved access to essential medicines (including blood and blood products), vaccines, diagnostics and devices for primary health care.

IRP are critically important for the development and standardization of the numerous biological and immunological assays (in vitro diagnostic assays, IVD) used for the diagnosis of diseases and a wide range of biologicals, including therapeutics, blood-derived products, vaccines and immunological products. As reference sources of defined biological activity expressed in an internationally agreed unit, they form the basis for a uniform reporting system, helping regulatory authorities, manufacturers, physicians and scientists to communicate in a common "language". Hence, IRP are widely used by regulatory authorities, in industry and also in biological research in academic and scientific organizations.

As high standards of efficacy, quality and purity, IRP are generally intended for use in the characterization of the activity of secondary reference preparations.

Status: ongoing

1.1 Development of the 1st WHO International Standard for Antibodies to Chikungunya Virus (CHIKV)

Chikungunya virus is an alphavirus that causes chikungunya fever. It is transmitted by mosquitoes of the Aedes genus. Chikungunya fever manifests itself predominantly through symptoms such as high fever, skin

rash, joint pain and arthritis, which can last for years. Every year, between 300.000 and over one million people are infected worldwide.

Dr Sally Baylis, PEI, developed a WHO International Standard (IS) for CHIKV-specific neutralizing antibodies (IgG). This IS was tested for its neutralizing activity towards different CHIKV genotypes. CHIKV has three main genotypes: West Africa (WA), East/Central/South Africa (ECSA), Asia and Indian Ocean Lineage (IOL). For this purpose, the envelope protein genes of the three CHIKV genotypes were synthesized, including the genotype most prevalent in Brazil, where large outbreaks occurred in the last years. The neutralizing properties of the IS were assayed by using lentiviral vectors containing the envelope proteins. WA, ECSA and IOL pseudo typed vectors were neutralized to a similar extend, showing that the IS is suitable as reference for all CHIKV genotypes.

The WHO Expert Committee on Biological Standardization (ECBS) adopted the candidate material as the 1st WHO International Standard for Antibodies to Chikungunya Virus (CHIKV) at the meeting in October 2022 (see also 2.1).

1.2 New Project: Development of the “WHO 1st International Reference Reagent for anti-Ross River Virus (Immunoglobulin G) Neutralizing Antibodies”

The new project, developed by Dr S Baylis and Dr B Schnierle was endorsed by the ECBS Committee in March 2023 (see 2.2).

Ross River virus (RRV) is a zoonotic member of the Alphavirus genus in the Togaviridae family and is transmitted by a variety of mosquito vectors including *Aedes* and *Culex* species. Ross River fever caused by RRV is the most common vector-borne disease in Australia; however, RRV was reported in Papua New Guinea and other Pacific regions including Fiji, the Cook Islands, American Samoa, New Caledonia, Wallis and Futuna, French Polynesia. Occasionally, RRV infections occur in travelers returning from endemic regions, and such importations may pose a potential risk of becoming established elsewhere - similar to other emerging arboviruses such as chikungunya virus and Zika virus. There is a large number of potential vertebrate hosts of RRV including both domestic and wild animals. Macropods such as kangaroos and wallabies seem to be the most important reservoirs of RRV, however, infections have been identified in cats, dogs, horses, bats and possums and human-mosquito-human transmission also occurs due to high levels of viraemia in people. The disease caused by RRV is characterized by rash, fatigue and polyarthralgia, which can last for weeks or months or even years – similar to closely related virus infections such as chikungunya fever.

Source/type of materials: Anti-RRV-positive plasma sourced through international collaborations; additional samples include negative plasma and plasma to evaluate Alphavirus cross-reactivity. All materials tested and confirmed negative for the presence of pathogenic blood borne viruses. ~3,000 vials of lyophilized plasma have been prepared from a plasma pool for anti-RRV antibody positive blood donors.

Outline of proposed collaborative study: Candidate reference reagent evaluation in an international collaborative study investigating potency and reactivity/specificity. Participating laboratories include: reference and academic laboratories, vaccine manufacturers, test kit providers and competent authorities using a range of RRV neutralization and immunoassays.

1.3 Participation in WHO Collaborative Studies for IVD

Unit Molecular Virology of PEI participated in the collaborative study CS712 to establish the 5th WHO International Standard for Hepatitis B (HBV) DNA for NAT-based assays as well as in CS714 for the establishment of the 2nd WHO International Standard for SARS-CoV-2 RNA for NAT-based assays. Both studies were organized by the National Institute for Biological Standards and Control (NIBSC), UK.

1.4 Participation in WHO Collaborative Studies for blood products

In 2022, PEI Unit HZG 3 – Product Testing Haematology, Cell and Gene Therapy, Division Haematology, Cell and Gene Therapy – participated in the collaborative studies to establish the 9th IS for Human Coagulation Factor VIII concentrate including the respective stability study (adoption by WHO ECBS in March 2023, and to establish the 6th IS for Human Coagulation Factor IX concentrate (adoption by WHO ECBS still pending). Both studies were organized by NIBSC.

1.5 Distribution and maintenance of WHO Reference Standards and Panels

So far, 17 WHO International Reference Preparations were developed by PEI colleagues and established by WHO ECBS.

Maintenance like stability studies and distribution as WHO Custodian Laboratory will be continued.

The activity is led by S Baylis, J Kress, A Filomena, K Nomo, K Himmelsbach, O Knauer, G Praefcke, M Prax, A Reißinger, H Scheiblauer, S Breitner-Ruddock, A Hunfeld, B Schnierle, M Nübling.

Activity 2

Title: Assist WHO with the development of two Non-endotoxin Pyrogen (NEP) reference reagents for the Monocyte Activation Test (MAT; Ph. Eur. 2.6.30.)

Description: WHO has emphasized its normative work in the “Thirteenth General Programme of Work 2019–2023” (GPW13): “What is new in GPW 13?”. WHO will strengthen its normative work. Setting norms and standards is a unique function and strength of WHO; it underpins the special position that WHO enjoys in global health, in which the Organization, through the Health Assembly, has the “authority to adopt conventions or agreements with respect to any matter within the competence of the Organization” as well as regulations and recommendations.” This activity contributes to the GPW 13 outcome 1.3, improved access to essential medicines (including blood and blood products), vaccines, diagnostics and devices for primary health care.

The International Pharmacopoeia is issued by the World Health Organization. The method described in biological methods 3.5 Test for Pyrogens currently undergoes major global changes (sustainability, animal protection). WHO is aware of these changes and will contribute its part to progress and welfare. In 2020, the WHO Committee on Biological Standardization (ECBS) underscored the importance of the monocyte activation test.

TRS 1030, p. 33:

“Acknowledging the need to incorporate the 3Rs principles into all WHO written standards for biological products, the Committee supported the inclusion of the monocyte activation test as an in vitro alternative to the rabbit pyrogenicity test.

Furthermore, the Committee suggested text to make it clearer that the need for pyrogenicity testing should be based on risk assessment.”

The Rabbit pyrogen test (RPT, Ph. Eur. 2.6.8.) will be replaced by the Monocyte Activation Test (MAT, Ph. Eur. 2.6.30.) in Europe and beyond. Both methods are used to detect fever-inducing substances (potentially causing severe effects in patients) in therapeutic and prophylactic products like sera and vaccines.

Globally there is substantial interest in the MAT in terms of vaccine testing. Moreover, the MAT is already mentioned in the Chinese and Indian Pharmacopoeia.

The introduction of high-quality WHO-NEP reference materials will support MAT-acceptance by regulators and users (as the WHO International Standards (IS) for Endotoxin 1-3 already did for the Bacterial Endotoxin Test (BET)).

Due to our long-lasting experience in developing and establishing the MAT (and establishing the rFC), including supportive work for the European Directorate for the Quality of Medicines & Health Care (EDQM), we acknowledge the need of non-endotoxin Pyrogen (NEP) reference reagents. They may be used to evaluate and compare the performance of different MAT assays for the detection of pyrogenic contaminants. Users will be test developers and laboratories performing the MAT.

Status: ongoing

Dr J Hubloher, PEI, (paid by the 3R-Grant of the German BMBF (Bundesministerium für Bildung und Forschung/ Federal Ministry of Education and Research) investigated several NEP-candidates in different MAT-setups (whole blood, PBMC, iPSC; rabbit whole blood) to achieve dose-response curves. Based on Dr Hubloher's findings the PEI proposed further NEP-candidates in addition to Pam3CSK4 to the NIBSC. Colleagues at NIBSC will include these candidates in their formulation trials. PEI will test some of the formulated candidates as soon as available.

Progress of the project was discussed during two video conferences between EDQM (European Directorate for the Quality of Medicines & HealthCare), NIBSC and PEI.

The activity is led by I Spreitzer, J Hubloher, M Prax, O Krut.

Activity 3

Title: Inform WHO's work in the development of written guidance documents for regulatory bodies and laboratories worldwide

Description: Provision of guidance is a core function of WHO, set out in its Constitution (Article 2). Since its establishment by constitution in 1948, WHO has played a key role in developing norms and written standards for the manufacturing, licensing, and control of blood products, and related in vitro diagnostic tests/technologies. Following globalization, international WHO guidance documents are of growing importance not only for low and middle-income countries (LMIC), but increasingly also for high-income countries (HIC). Consequently, the normative function of WHO has been emphasized in the "Thirteenth General Programme of Work 2019–2023" (GWP13) of WHO. This activity contributes to the GPW 13 outcome 1.3, improved access to essential medicines (including blood and blood products), vaccines, diagnostics and devices for primary health care.

The development of WHO guidance documents is based on international consensus resulting from consultations with the international scientific and professional communities, regulatory authorities, manufacturers and experts worldwide. As per 1947, they are finally discussed and adopted by the WHO Expert Committee on Biological Standardization (ECBS).

The guidance documents are intended to assist WHO Member States in ensuring consistent quality and safety of biological medicines and related in vitro biological diagnostic tests.

Status: ongoing

3.1 The WHO 1st International Standard for SARS-CoV-2 Immunoglobulin had been prepared in short time frame by NIBSC, followed by establishment by ECBS in 2020. The potential user community struggled with appropriate use of the material developed both for standardization of neutralization assays and for harmonization of antibody binding assays. An ad hoc Working Group was installed by WHO to discuss and prepare proposals to ECBS for future approaches for antibody standards containing a variety of different, though related, analytes, e.g. antibody-dependent functional activity, antigen-specific binding activities representing immunoglobulin subclasses. Proposals for unitage assignments for respective preparations were presented to ECBS in March 2023 by Dr M Nübling, PEI, on behalf of the Working Group.

3.2 Dr W Samukange of PEI participated in the Working Group for the revision of the "WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices". WHO Medical device technical series; replacement of Annex 4 of WHO Technical Report Series (TRS), No. 1003. The revision was adopted by ECBS in October 2022 (see also 2.1).

3.3 Dr B Klug, PEI, participated in the Working Group for drafting the "WHO Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related biological products intended for the prevention or treatment of human infectious diseases". The guidelines were adopted by ECBS in March 2023 (see 2.1). The TRS report is pending.

The activity is led by M Nübling, J Atemnkeng, I Bekerredjian-Ding, J Blümel, S Breitner-Ruddock, A Filomena, S Groß, K Heinrich, S Heinz-Stempel, A Hunfeld, C Kafere, M Doll, O Knauer, J Kress, M Prax, J Reinhardt, A Reißinger, H Scheiblaue, B Schnierle.

Activity 4

Title: Support WHO in organizing training workshops related to the “Achilles Project”, i.e. “Improving Access to Safe Blood Products through Local Production and Technology Transfer in Blood Establishments”

Description: In 2008, the so-called Achilles Project was endorsed by the WHO Expert Committee on Biological Standardization (ECBS). WHO undertakes the project to enable low and middle-income countries (LMICs) to make use of blood components currently discarded as biological waste.

The project should increase access, especially for the poor in developing and least developed countries, to life-saving plasma derivatives, e.g. coagulation factor concentrates.

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 Blood Regulators Network (BRN), e.g. by elaborating the document “Assessment Criteria for National Blood Regulatory Systems”.

A WHO Guidance on “Increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma” for revival of the Achilles Project was written (Feb.-Jul. 2020), with PEI (Micha Nübling) being represented in the drafting group. This document is expected to convince policy makers on the key steps to be taken to enable the use of recovered plasma as valuable source for life saving medicines. This activity will also contribute to the GPW 13 outcome 1.3, improved access to essential medicines (including blood and blood products), vaccines, diagnostics and devices for primary health care.

Status: ongoing

During the reporting period, under the umbrella of the Global Health Protection Programme (GHPP “BloodTrain” project, initiated by the German Ministry of Health in 2016) there were no activities performed on behalf of WHO.

The activity is led by M Nübling, J Atemnkeng, A Filomena, K Heinrich, S Heinz-Stempel, A Hilger, C Kafere, O Knauer, J Kress, M Prax, J Reinhardt, A Reißinger, S Ring, H Scheiblaue.

Activity 5

Title: Support WHO in the assessment of blood regulation using WHO Global Benchmarking Tool plus Blood

(GBT plus Blood) and respective training activities on the use of the GBT plus Blood, upon WHO’s request

Description: WHO developed the Global Benchmarking Tool (GBT) and the Institutional Development Plan (IDP), pursuant to WHO Resolution 67.20 to evaluate the performance level and to build the pathway towards the advanced level, where necessary. However, performing the assessments is time consuming and needs experts in the regulatory field, and this work cannot be performed by WHO alone. This activity will support WHO by providing assistance in performing, assessments with the GBT and supporting the integration of indicators and sub-indicators for blood regulation into the ‘GBT plus Blood’.

The ‘GBT plus Blood’ assessments will help the corresponding regulatory authorities to see in which areas the regulatory system needs strengthening and to build an IDP to achieve it. This activity will also contribute to the GPW 13 outcome 1.3, improved access to essential medicines (including blood and blood products), vaccines, diagnostics and devices for primary health care.

WHO may, as and when appropriate, use the deliverables to evaluate the current state of regularly strength and need for additional support in the participating countries. This will also help to evaluate what is needed in a given region to build a network of reliant regulatory authorities to make better use of limited resources within the regulatory systems of a region, e.g. by forming reliant networks for regulatory activities like inspections or drug licensing.

The ‘GBT plus Blood’ also constitutes a valuable tool for self-assessment. Trainings supported by the institution will help increase the number of regulatory authorities profiting from the ‘GBT plus Blood’.

Status: ongoing

During the reporting period, WHO did not ask for support in the assessment of blood regulation using WHO Global Benchmarking Tool plus Blood (GBT plus Blood) and respective training activities.

The activity is led by J Reinhardt, A Hilger, J Atemnkeng, K Heinrich, C Kafere, M Nübling.

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 76th Meeting of the Expert Committee on Biological Standardization (ECBS), Geneva, Switzerland, (virtual meeting), 24-28 Oct. 2022

The President of the PEI, Professor Cichutek, acted as a chairperson of the ECBS (Plenary/Vaccines Track). Dr M Nübling and Dr G Unger participated in the meeting as well.

The Blood Track meeting focused on the "Revision/update of the WHO Global Model Regulatory Framework for Medical Devices (including IVDs)". The revision was discussed and finally adopted. Dr W Samukange of PEI participated in the Working Group (see Activity 3).

The 1st WHO International Standard for Antibodies to Chikungunya Virus (CHIKV), developed by PEI was proposed as WHO international standard and adopted by the Committee (see Activity 1).

The entire activities of the ECBS October 2022 meeting are laid down in the WHO Technical Report Series (TRS 1045).

2.2 77th Meeting of the Expert Committee on Biological Standardization (ECBS), Geneva, Switzerland, (virtual meeting), 20-24 Mar. 2023

The President of the PEI, Professor Cichutek, acted as a chairperson of the ECBS (Plenary/Vaccines Track). Dr S Baylis, Dr A Hilger, Dr M Nübling, and Dr G Unger also participated in the meeting.

The "WHO Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related biological products intended for the prevention or treatment of human infectious diseases" was discussed and adopted by the Committee. Dr B Klug, PEI, participated in the Working Group (see Activity 3).

Dr S Baylis presented a new proposal for the development of the "WHO 1st International Reference Reagent for anti-Ross River Virus (Immunoglobulin G) Neutralizing Antibodies" (see Activity 1). The ECBS Committee endorsed the project.

2.3 WHO Advisory Group on Blood Regulation, Availability and Safety (AG BRAS)

In July 2021, Dr A Hilger was appointed Chair of the WHO Advisory Group on Blood Regulation, Availability and Safety.

AG BRAS succeeds the Blood Regulators Network (BRN).

As an advisory body to WHO, its functions are described as follows (<https://www.who.int/news-room/articles-detail/call-for-experts-advisory-group-on-blood-regulation-availability-and-safety>):

- To advise on the development of WHO norms, standards, technical guidelines and high-level strategic recommendations on ensuring safety, quality and availability of blood products.
- To advise on scaling up the implementation of existing WHO policies, strategies, including innovative strategies and tailored approaches; as well as strengthening the national systems for blood supply and regulation to achieve the goal of universal access to safe, effective and quality assured blood products.
- To provide scientific assessment of current and emerging threats to the safety and availability of blood and

blood products; to advise on the recommended measures and actions to be taken by the Member States in preparedness for and in response to the emerging public health threats.

Since its implementation, nine plenary meetings took place as well as numerous working subgroup meetings. A face to face meeting of the group took place at WHO Headquarters, Geneva on 7-8 March 2023.

2.4 Cooperation with WHO in the area of WHO's Prequalification Programme (PQ) for in vitro Diagnostic Devices (IVDs) and Procurement of IVDs
Experts from PEI continued to participate in the WHO Prequalification of Diagnostics (PQDx) programme.

2.4.1 Review of product dossier submissions of in vitro diagnostic devices (IVD) for the WHO Prequalification Programme (PQDx) / WHO for Emergency Use Listing (EUL) of IVDs for the diagnosis of SARS-CoV-2
Against the background of the COVID-19 pandemic, one dossier review for one SARS-CoV-2 RT-PCR Test kit was performed within the WHO Emergency Use Listing procedure by Dr K Esser-Nobis, Section PEI-IVD Testing Laboratory.

2.4.2 Training for IVDs assessors and Meeting of WHO Prequalification, ERPD (Expert Review Panel for Diagnostic Products) and EUL of In Vitro Diagnostics Experts, WHO Headquarters (hybrid), 2-5 May 2023
Dr K Esser-Nobis, Dr A Filomena, Dr A Reißinger, and Dr M Nübling participated in the training as well as in the meeting (online participation).

2.5 International Nonproprietary Names (INN) of blood products and monoclonal antibodies
From July 2022 to June 2023, Dr K Weisser assessed 274 INN requests of biological and 180 INN requests of chemical substances. She attended two consultations of the INN expert group (74th consultation, October 2022; 75th consultation, March 2023), where new and outstanding applications were discussed and decisions on the selection of INNs were taken.
She also attended the School of INN (SoINN) pilot site meeting on 24-25 May 2023 at the University of Grenoble, France. The main objectives of the meeting were to brainstorm on how to increase the awareness of the WHO INN programme and further develop the SoINN project.

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
30	23	0

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

Senior staff	Mid-career staff	Junior staff, PhD students
232	262	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 Cooperation with the WHO Collaborating Centre National Institute for Biological Standards and Control (NIBSC), UK

At the 75th WHO ECBS-Meeting 2022, the project “Assist WHO with the development of two Non-endotoxin Pyrogen (NEP) reference reagents for the Monocyte Activation Test (MAT; Ph. Eur. 2.6.30.)” was endorsed (see Activity 2). Cooperation with NIBSC was agreed.

The European Directorate for the Quality of Medicines and HealthCare (EDQM), which is also interested in the project, PEI and NIBSC are in regular contact to share information on the progress of the activity.

4.2 (Virtual) Meetings of WHO Collaborating Centres (CCs) to support the development of WHO Biological Reference Preparations for Blood Products and in vitro Diagnostic Devices

During the reporting period, WHO did not schedule a meeting of the WHO Collaborating Centres.