Collaborating Centres ANNUAL REPORT

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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	07-2021 to 07-2022		

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
Development of the 1st International Chikungunya Virus (CHIKV) Reference Reagent for Serology
The development of the 1st International Chikungunya Virus (CHIKV) Reference Reagent for Serology has been finalized by Dr S Baylis and colleagues. A draft report has been sent to WHO for consideration by the WHO Expert Committee on Biological Standardization, ECBS, at the October 2022 meeting.

Participation in WHO Collaborative Studies for in vitro Diagnostic Devices
Participation in the WHO Collaborative Studies for Establishment of the 2nd WHO International Standard for Anti-SARS-CoV-2 Immunoglobulin
The studies were led by the National Institute for Biological Standards and Control (NIBSC), UK, PEI participation by Dr K Esser-Nobis, PEI-IVD Testing Laboratory.

Participation in the WHO Collaborative Studies for Establishment of the 1st WHO International Standard for SARS-CoV-2 Antigen
Led by the NIBSC, PEI participation by Dr C Steffanowski, PEI-IVD Testing Laboratory.

Participation in WHO Collaborative Studies for blood products
In 2021/2022, the PEI Section Batch Release of Blood Products, Logistics, Division Haematology participated in the collaborative studies to establish the 3rd WHO IS for von Willebrand factor concentrate (adoption by WHO ECBS in October 2021) and the 2nd WHO IS for Factor XIII, plasma (adoption by WHO ECBS still pending). Both studies were organized by the NIBSC.

Distribution and maintenance of WHO Reference Standards and Panels
So far, 15 WHO International Reference Preparations have been developed by PEI colleagues and established by WHO ECBS.
Maintenance such as stability studies and distribution as WHO Custodian Laboratory will be continued.

This activity is led by S Baylis, J Kress, A Filomena, S Hanitsch, K Himmelsbach, O Knauer, J Mitterreiter, 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
The project was presented for endorsement at the 75th WHO ECBS-Meeting 2022 on 7 April 2022 as topic no. 18. The committee agreed on the endorsement. Cooperation with NIBSC was agreed.
The current status of the project is that both the PEI and the NIBSC have to regain full operational capability (loss of staff, reorganizations) to fully cooperate on the project. The European Directorate for the Quality of Medicines and HealthCare (EDQM), the PEI and the NIBSC are in close contact and will establish regular exchanges on the form and progress of the project.

This activity is led by I Spreitzer, 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
The WHO 1st International Standard for SARS-CoV-2 Immunoglobulin was prepared in a short time frame by the 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 explanatory article was drafted by an expert group (including Dr M Nübling, PEI) and published in a peer-reviewed, high-ranking journal.
Knezevic I, Mattiuzzo G, Page M, Minor P, Griffiths E, Nuebling M, Moorthy V (2021) WHO International Standard for evaluation of the antibody response to COVID-19 vaccines: call for urgent action by the scientific community. The Lancet Microbe. https://doi.org/10.1016/S2666-5247(21)00266-4.

Furthermore, PEI colleagues volunteered to re-emphasize the use of the International Unit for NAT assays designed for pathogen testing, focusing on the clinical chemistry community and on the recently established WHO IS for SARS-CoV-2 RNA. This attempt resulted in a "News & Views" article in another peer-reviewed, high-ranking journal.
Baylis SA, Nübling CM (2022) Nucleic Acid Testing of Viral Pathogens: Traceability of the International Unit. Clinical Chemistry 68:257-258. DOI:10.1093/clinchem/hvab114

Another publication in a scientific virology encyclopaedia summarizes standardization issues for diagnostic tests, highlighting the WHO approach in this field.
Baylis SA, Nübling CM, Dimech W. (2021) Standardization of diagnostic assays. Editor(s): D. H. Bamford, M. Zuckerman, Encyclopedia of Virology (Fourth Edition), Academic Press,pp 52-63. ISBN 9780128145166, https://doi.org/10.1016/B978-0-12-814515-9.00092-8

This activity is led by M Nübling, J Atemnkeng, I Bekeredjian-Ding, J Blümel, S Breitner-Ruddock, A Filomena, S Groß, K Heinrich, S Heinz-Stempel, A Hunfeld, C Kafere, M Doll, O Knauer, J Kerr, J Kress, HA Mbunkah, M Prax, J Reinhardt, A Reißinger, W Samukange, H Scheiblauer, 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) related activities were performed, such as active participation in
- the WHO Regional Self-Benchmarking for Blood Regulation (virtual) meeting, 26-30 July 2021. W Samukange, K Heinrich, J Atemnkeng, and C Kafere, PEI, GHPP “BloodTrain”, acted as facilitators;
- the WHO Regional Workshop on Establishing National Haemovigilance Systems (virtual) meeting, 10-12 November 2021. Attendance by W Samukange, PEI GHPP.

Furthermore, W Samukange, M Nübling, and J Engelbergs of the PEI participated in the revision of the “WHO Global Model Regulatory Framework for Medical devices including in vitro diagnostic medical devices” (GMRF) (meetings every two weeks, Sept. 2021-Jun. 2022) (latest version now available for public consultation);

In addition, drafting of the “WHO User guide for navigating resources on stepwise implementation of haemovigilance systems” was supported by W Samukange, PEI. The draft was reviewed i.a. by A Hilger, PEI. The guideline was published in July 2022, https://www.who.int/publications/i/item/9789240047860.

This activity is led by M Nübling, J Atemnkeng, A Filomena, K Heinrich, S Heinz-Stempel, A Hilger, C Kafere, O Knauer, J Kress, HA Mbunkah, M Prax, J Reinhardt, A Reißinger, S Ring, W Samukange, H Scheiblauer.

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, HA Mbunkah, W Samukange, 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 thatwas not requested by and agreed with WHO.

2.1 74th Meeting of the Expert Committee on Biological Standardization (ECBS), Geneva, Switzerland, (virtual meeting), 18-22 Oct. 2021
The President of the PEI, Professor Cichutek, acted as chairperson of the ECBS (Plenary/Vaccines Track). Dr A Hilger, Dr M Nübling and Dr G Unger participated in the meeting.
The virtual meeting focused again on issues related to the SARS-CoV-2 pandemic.
The guideline "Evaluation of the quality, safety and efficacy of messenger RNA vaccines for 9 the prevention of infectious diseases: regulatory considerations", was extensively discussed in plenary sessions.
The entire activities of the ECBS October 2021 meeting are laid down in the WHO Technical Report Series (TRS 1039).

2.2 75th Meeting of the Expert Committee on Biological Standardization (ECBS), Geneva, Switzerland, (virtual meeting), 4-8 Apr. 2022
The President of the PEI, Professor Cichutek, acted as chairperson of the ECBS (Plenary/Vaccines Track). One important topic was the adoption of a "WHO manual for the establishment of national and other secondary standards for antibodies against infectious agents focusing on SARS-CoV2".
Dr A Hilger, Dr M Nübling, Dr I Spreitzer, and Dr G Unger participated in the meeting.

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).
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, five plenary meetings have taken place as well as numerous working subgroup meetings.

2.4 Cooperation with WHO in the area of WHO´s Prequalification Programme (PQ) for in vitro Diagnostic Devices (IVDs) and the Emergency Use Listing (EUL) of IVDs

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
In the context of the Covid-19 pandemic, two dossier reviews for SARS-CoV-2 antigen rapid assays were performed within the WHO Emergency Use Listing procedure, both by section PEI-IVD (Dr K Esser-Nobis and Dr A Filomena).

One review of a post EUL listing product dossier for a SARS-CoV-2 semi-automated qualitative in vitro nucleic acid amplification test was performed (Dr M Nübling).

2.4.2 Assessor training for Emergency Use Listing (EUL) of IVDs for the Diagnosis of SARS-CoV-2, (virtual meetings), 8 and 15 Dec. 2021
Dr C Steffanowski, Dr K Esser-Nobis and Dr A Filomena participated in the training for new EUL assessors.

2.5 International Nonproprietary Names (INN) of blood products and monoclonal antibodies
From July 2021 to June 2022, Dr K Weisser assessed 283 INN requests of biological and 206 INN requests of chemical substances. She attended two WebEx-consultations of the INN expert group (73rd consultation, October 2021; 74th consultation, April 2022), where new and outstanding applications were discussed and decisions on the selection of INNs were taken.
She was head of a working group for monoclonal antibodies that has developed and proposed a new naming scheme, thus terminating the era of INN names ending with –mab. The new scheme was adopted by the INN expert group in the October 2021 consultation.

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	18	0

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

Senior staff	Mid-career staff	Junior staff, PhD students
314	246	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 (Virtual) Meetings of the WHO Collaborating Centres (CCs) IVD Network
8th Meeting of the WHO Collaborating Centres to Support the Development of WHO Biological Reference Preparations for in vitro Diagnostic Devices and Blood Products, (virtual meeting), 13 Sept. 2021.
The PEI CC was represented by A Filomena, C Kafere, J Kress, H Mbunkah, M Nübling, M Prax, A Reissinger, J Reinhardt, H Scheiblauer, I Spreitzer and E Zojer-Fuchs.

4.2 (Virtual) Meetings of the WHO Collaborating Centres (CCs) Blood and Transfusion Safety Network
Meeting of WHO Collaborating Centres for Blood and Transfusion Safety, (virtual meeting), 18-19 May 2022.
K Heinrich, J Reinhardt and W Samukange of the PEI Global Health Protection Programme (GHPP "BloodTrain") participated in the meeting.