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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 20 – 24 April 2026

Requests to initiate new/replacement WHO reference material projects for biologicals

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposal(s) contained therein. Written comments on the proposal(s) MUST be received in English by **23 March 2026** and should be addressed to:

Product Standards, Specifications and Nomenclature
Department of Medicines and Health Products Policies and Standards
World Health Organization
1211 Geneva 27
Switzerland

Comments may also be submitted electronically to **Dr Ivana Knezevic** at email: knezevici@who.int.

The distribution of this document is intended to provide information to a broad audience of potential stakeholders and to improve the transparency of the consultation process. Following consideration of all comments received, the proposal(s) will then be considered by the WHO Expert Committee on Biological Standardization (ECBS) prior to a final decision being made and published in the WHO Technical Report Series.

Proposed new/replacement projects

1. WHO International Reference Reagent for anti-HLA serum and anti-HPA antibody negative control for Luminex and flow cytometry crossmatch assays

2. WHO International Reference Reagents for immuno-monitoring assays

3. First WHO International Standard for autoantibodies to glomerular basement membrane

4. First WHO International Standard for measurable residual disease quantitation in acute myeloid leukaemia

5. First WHO International Standard for circulating tumour DNA

6. First WHO International Standard for antibodies to Oropouche virus

7. Second WHO International Standard for meningococcal serogroup X polysaccharide

8. Second WHO International Reference Panel for antibodies to human immunodeficiency virus

9. Third WHO International Standard for granulocyte colony stimulating factor

Anti-HLA serum and anti-HPA antibody negative control for Luminex and flow cytometry crossmatch assays

Proposal (title)	WHO International Reference Reagent for anti-HLA serum and anti-HPA antibody negative control for Luminex and flow cytometry crossmatch assays		
Proposer (name of Institution)	MHRA	**Principal contact**	Sandra Prior/Edward Smith/Anna Nowocin
Rationale	The presence of donor-specific anti human leucocyte antigen (HLA) antibodies in transplant recipients can lead to rejection and therefore, evaluation of potential recipients for anti-HLA antibodies is crucial for successful transplantation outcomes. Flowcytometric and bead-based Luminex assays are sensitive in detection of pre-sensitization in potential transplant recipients and are widely used in clinical histocompatibility and Immunogenicity (H&I) labs and Blood Services. Anti-HLA controls have been manufactured and available from NIBSC since 2001, as CE marked products from 2018, and recently since 2023 as WHO IRR. These reagents are widely used and are essential as controls in pre- and post-transplant alloantibody screening for donor/recipient organ/tissue matching as well as investigating adverse transfusion-related reactions performed by clinical labs globally. WHO anti-HLA international reference reagents as negative, strong positive and weak positive controls for anti-HLA antibody assays are available and typically used in two highly variable assay platforms, namely Flow cytometry crossmatching (FCXM) and alloantibody Luminex (LX) assays, that are routinely used to assess alloreactivity of donor/recipient and make clinical decisions related to organ and tissue transplantation in patients. Currently, the WHO anti-HLA negative controls, 10/142 and 17/212, plasma and serum products respectively, are rapidly depleting, and a new negative preparation needs to be developed to ensure continuity of supply. Recently, other non-HLA antibodies such as anti-HNA (human neutrophil antigen) and anti-HPA (human platelet antigen) antibodies have been associated with transfusion-related acute lung injury (TRALI), neonatal alloimmune neutropenia (NAN) and kidney transplant rejection and are also investigated in the pre- and post-transplant and transfusion context in clinical specialised laboratory units. Further, laboratories using WHO anti-HLA controls have enquired on the suitability of current anti-HLA negative controls as anti-HNA negative controls, and moreover, several collaborators and experts in the field have indicated the utility of a dual anti-HLA and anti-HNA negative control or a universal negative control for cross matching and bead-based antibody detection assays. In view of the interest for a dual or universal negative control, the new preparation will be composed of pooled human sera from new donors, therefore this preparation will be regarded as a new standard rather than a replacement product, and the new candidate will also be assessed for anti-HNA and where possible, anti-HPA antibodies with the aim to extend the use of the preparation to also non-HLA antibody detection assays. Further,		

	note that we will not be seeking developing plasma anti-HLA (or as extended negative control) products but only anti-HLA sera products (or as extended negative controls) as per current alloreactivity testing guidelines.		
Anticipated uses and users	As controls in Flow cytometry crossmatching (FCXM) and alloantibody Luminex assays used by H&I labs and transfusion services in the UK and globally.		
Source/type of materials	Pooled of human AB sera from male, non-transfused donors of a diverse ethnic background (self-claimed) from NHSBT or commercial suppliers.		
Outline of proposed collaborative study	The international collaborative study will involve performance of FCXM and Luminex single antigen as well as/or screen assays by us and by at least 10 other H&I labs across different countries and continents. The labs will use the candidate negative control preparation along their clinical and in house control samples, and other NIBSC controls. Raw MFI data or coded CSV files will be returned for analysis in NIBSC.		
Issues raised by the proposal	None to date.		
Action required	ECBS to endorse proposal.		
Proposer's project reference		**Date proposed:**	1 February 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	Flow cytometry cross matching (FCXM) and Luminex bead assays with broad HLA Class I and II allotype coverage are routinely used by H&I clinical laboratories to make clinical decision on donor/recipient alloreactivity for transplantation. The use of these assays and run controls (NIBSC) is described in the "Guidelines for the Blood Transfusion Services: Chapter 16: HLA typing and HLA serology; 16.7: Leucocyte crossmatching in blood transfusion; Annexe 1: NIBSC standards available from MHRA" http://www.transfusionguidelines.org/red-book/		
Number of products or methods	Currently, FCXM using donor/recipient PBMCs is used and two main Luminex single antigen bead assays for HLA alloantibody profiling are commercialised and marketed: One lambda/ThermoFisher Labscreen and Immunocor Lifecodes LSA. These will be used in house and by participants in the collaborative study.		
Public health importance	WHO Anti-HLA reference reagents (RR) for Flow Cytometry Crossmatch (FCXM) and Luminex (LX) antibody assays are used as run controls to validate and harmonize assays for alloantibody detection These reagents crucially influence the delivery of assays that impact on clinical decisions related to organ and tissue transplantation in patients.		

Global importance	Establishment of WHO anti-HLA (or extended negative control) RRs supports global accessibility, widen availability to user labs involved in organ transplantation programs within and outside EEA and thereby, aid global public health. Continuity of supply is essential to fulfil this role. Some clinical laboratories may have access to relevant serum from geographic area specialised reference laboratory units to prepare or share controls, however, many rely on the use of WHO IRRs.
Global need from regulatory & scientific considerations	The global availability of independent WHO anti-HLA (or extended negative) controls tested internationally is important to both ascertain the suitability of assays used in clinical decisions during transplantation and facilitate harmonisation.
ECBS outcome	[BLANK]

Immuno-monitoring assays

Proposal (title)	WHO International Reference Reagents for immuno-monitoring assays		
Proposer (name of Institution)	MHRA	**Principal contact**	Sandra Prior/Deepa Rajagopal
Rationale	Cell-mediated immunity (CMI) is a fundamental component of the body's defence against infectious diseases and cancer. Effective vaccines and immunotherapies rely on both humoral (antibody-mediated) and cellular immune responses. While antibodies produced by B cells can neutralise pathogens, T cells play a crucial role in supporting antibody production and directly eliminating infected or abnormal cells. Increasing evidence demonstrates that both arms of the immune system are essential for robust and lasting protection, whether following natural infection or vaccination. Despite this, the identification and measurement of cell-mediated immune responses remain challenging. Most vaccines are currently approved based on data from humoral responses, as these are easier to measure and standardise. In contrast, assessing antigen-specific T cell responses is complicated by several factors including: the complexity and cost of cell-based assays, the need for high-quality cell samples and study designs that reflect diverse HLA types, ages, and demographic and limited sample availability and a lack of harmonised procedures, which hinder the validation and comparison of results across studies and laboratories. Currently, T cell response assessments are typically limited to small donor cohorts in early-phase clinical trials. This restricts our understanding of the role of CMI as a biomarker and its potential as a correlate of protection—information that could inform the development of new vaccines and immunotherapies. Among available methods, ELISpot (and newer variant FluorSpot) and intracellular cytokine staining (ICS) assays are considered gold standards for measuring antigen-specific T cell responses and are widely used in clinical immune-monitoring. ELISpot has been used for decades and is valued for its sensitivity and relative simplicity, detecting cytokine-secreting T cells in peripheral blood mononuclear cells (PBMCs) after antigen stimulation. Most often used in parallel, ICS assays by flow cytometry allow for detailed immunophenotyping but are considered by some as less sensitive. ICS assays can be labour-intensive and focus on the measurement of intracellular cytokines in stimulated cells treated with transport inhibitors following fixation and permeabilization. Progress in the field has been supported by published guidelines, international consortia, and proficiency testing programmes. Initiatives such as the Coalition for Epidemic Preparedness Innovations (CEPI) centralised laboratory network have contributed to harmonised vaccine assessment. However, the absence of public reference standards continues to impede inter-laboratory and multi-site comparisons. This was evident during the COVID-19 pandemic, where the lack of T cell reference reagents limited the comparability of cellular immunity data, in contrast to serological studies that benefited from WHO international standards. The recent discontinuation of key proficiency panel programmes—originally established by the US Cancer Immunotherapy Consortium (CIC) and the		

	European Association for Cancer Immunotherapy (CIMT) and later provided by Immudex—further exacerbates the challenge. These programmes have played a significant role in external validation and harmonisation of T cell assays worldwide for years. Given these challenges, there is a clear and urgent need for WHO reference reagents to support the standardisation and global harmonisation of ELISpot and ICS assays. Such reagents would facilitate reliable, comparable assessment of cell-mediated immune responses.
Anticipated uses and users	As controls in ELISpot and Intracellular staining (ICS) in flow cytometry assays by laboratories that perform immuno-monitoring assessment worldwide.
Source/type of materials	Cell lines and/or human primary cells developed in house or obtained from commercial suppliers, that may produce one or more relevant cytokines constitutively or after polyclonal or specific antigenic stimulation.
Outline of proposed collaborative study	The international collaborative study will involve performance of ELISpot and ICS assays by at least 10 laboratories across different countries and continents. The labs will use the candidate control preparation(s) alongside their in-house control samples. Raw data will be returned for analysis in NIBSC.
Issues raised by the proposal	None to date, although some forecast challenges relate to the production of a big enough batch of cells to prepare the candidate material as a cryopreserved viable and functional cell preparation.
Action required	ECBS to endorse proposal.

CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Proposer's project reference		**Date proposed:**	1 February 2026
Approval status of medicine or in vitro diagnostic method	Vaccine induced CMI investigation is a regulatory requirement during development and in clinical trials. However, typically, T cell immunity data is most often exploratory and/or used as supportive evidence in regulatory submissions[1] due to the limited findings from small donor cohorts in early clinical trials, influenced by the challenges associated with sample collection, processing and poor method standardisation. At times when provided data to regulators, this is not amenable to be used in regulatory decisions. The importance of developing robust and harmonised clinical immuno-monitoring methods that help decreasing variability across laboratories, reduce technical challenges and allow more meaningful and larger data sets is increasingly acknowledged by developers and regulators. Progress in the field will facilitate a better understanding of vaccine-induced T cell responses, correlates of protection, and the implementation of most optimal vaccine strategies[1].		

	ELISpot and ICS assays are used in the study of immune responses to prophylactic vaccines for infectious diseases but are also extensively used in the assessment of cancer vaccine efficacy. More recently these methods have been useful to gain insights on efficacy and safety of new cell and gene therapies like CAR-T cell, AAV gene therapies, and in personalised medicine, where a comprehensive immuno-analysis is essential and cytokine secretion assays are an important tool. [1]Buoninfante A and Cavaleri, M. (2025) T cell responses after vaccination: a regulatory perspective. Front. Immunol. 16:1584738. doi: 10.3389/fimmu.2025.1584738.
Number of products or methods	Currently, ELISpot and ICS by flow cytometry are the gold standard assays used in clinical immuno-monitoring, most often used in parallel as offering complementary and crucial insights. The assays will be performed in house and by participants in the collaborative study. Other assays will also be considered.
Public health importance	Understanding the contribution of CMI to vaccines and immuno-therapies is paramount to gain deeper insights on correlates of protection, efficacy and potential immune-driven safety effects for advancements in the design and development of better and safer biologics. Our understanding of cellular immune responses across studies and products depend greatly on the availability of robust and standardised methods and therefore the support of publicly available reference reagents and controls. The availability of WHO reference reagents for Immuno-monitoring (ELISpot and ICS assays) would support harmonisation and promote advances in the regulation and design of biologicals that modulate cellular immune response and impact the availability of improved biologicals for patients. Further, the role of these reagents will be particularly important whilst no proficiency panel programs are available.
Global importance	Clinical trials are typically conducted in different countries and samples are shipped and analysed in different laboratories often across countries and multiple study sites. The establishment of WHO reference reagents for ELISpot and ICS assays would support global access to tools that will promote assay validation and global harmonisation and therefore aid global public health. Supporting assays worldwide would potentially also improve the quality and breath of data generated by potentially including broader genotypic diversity that is essential to understand Ag-specific cellular responses.
Global need from regulatory & scientific considerations	The global availability of independent WHO reference reagents for assays used in immuno-monitoring will support the findings from these assays for filing regulatory applications and the interpretation of clinical data by regulators and developers to gain a better understanding of CMI associated with response to vaccines and therapies. By facilitating the interpretation and quality of the data generated by these classical assays and potentially other assays, the field will have a better chance to evolve towards utilising T cell response focused immunogenicity endpoints, which currently do not exist for any approved vaccine.
ECBS outcome	[BLANK]

Autoantibodies to glomerular basement membrane

Proposal (title)	First WHO International Standard for autoantibodies to glomerular basement membrane		
Proposer (name of Institution)	MHRA/JRC	**Principal contact**	Dina Vara
Rationale	Glomerular basement membrane autoantibodies generally referred to as anti-GBM disease, are categorised as a rare autoimmune condition. These autoantibodies attack the glomerular basement membrane (GBM) in the kidneys and/or the alveolar basement membrane (ABM) in the lungs. When both the lungs and kidneys are affected, the condition is commonly known as Goodpasture's syndrome, typically manifesting as pulmonary haemorrhage and glomerulonephritis. The disease predominantly affects two demographic groups: young individuals aged 20 to 30 and older adults in their 60s and 70s. Males are slightly more frequently affected than females. GBM autoantibodies serve as a highly sensitive and specific indicator of Goodpasture's syndrome. The pathogenic autoantibodies are predominantly of the IgG class. Their levels are associated with disease activity and frequently serve as predictors of clinical outcomes. GBM autoantibodies are present in the serum of most patients diagnosed with Goodpasture's syndrome. Consequently, the diagnosis relies on detection methods, such as enzyme-linked immunoassay (ELISA), chemiluminescence, and protein electrophoresis. In instances where patients lack identifiable circulating antibodies through serologic testing, renal biopsies are performed for the immunofluorescence detection of IgG, which identifies the same autoantibodies in situ. Quantitative, commercially available diagnostic test kits for the measurement of these autoantibodies exhibit variability in results between different laboratories due to factors like inter-assay variation and the nature of autoantibody detection. In addition, controls and calibrators supplied with these kits have arbitrarily assigned unitage (U/mL, ng/Ml, RU/mL). Calibration with an International Standard would improve the comparability of results from different tests, facilitating the use of GBM autoantibodies as diagnostic markers of Goodpasture's syndrome, and would improve the monitoring of the disease management.		
Anticipated uses and users	An GBM autoantibody IS would be used by diagnostic kit manufacturers to calibrate their internal standards and by research institutions. Commercially available assays for GBM autoantibodies are used on a global scale and in the NHS clinical laboratories in the UK.		
Source/type of materials	The GBM autoantibody starting material was a serum produced from plasmapheresis material obtained from one consenting patient with Goodpasture's syndrome. The material was tested and found negative for all major pathogens (Hepatitis B surface antigen, HIV 1&2, HIV antigen, Hepatitis C) antibodies. The JRC intend to establish this material as a Working Standard made available from their catalogue. A proportion of the material will be		

	established as the 1st WHO International Standard with units assigned in IU/vial.		
Outline of proposed collaborative study	The lyophilised candidate IS material will be provided to manufacturers and diagnostic laboratories to evaluate using assays they use in their laboratory. The commutability of the candidate IS will also be evaluated against patient samples to determine suitability as a reference material.		
Issues raised by the proposal	Producing a commutable standard. The material was prepared using the argon method of drying and preserving lyophilised products. Thus, there may be challenges in measuring the oxygen headspace. However, we have prepared argon standards to help to determine oxygen measurements.		
Action required	ECBS to endorse proposal.		
Proposer's project reference		**Date proposed:**	1 February 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	FDA cleared and CE-marked in vitro diagnostic kits are commercially available, some of which are designed for automated platforms.		
Number of products or methods	ELISA assays (e.g., from Euroimmun, Orgentec, INOVA, AESKU) and ELISA CLIA, and FEIA methods in automated platforms (e.g., Autobio, Euroimmun, Sebia, Thermo Fisher, Werfen).		
Public health importance	High. The measurement of GBM autoantibodies in patient blood is used in the diagnosis of anti-GBM disease and for regular monitoring of the disease management.		
Global importance	The incidence of the anti-GBM disease is approximately 0.5 to 1.8 cases per million per year in Asian and European populations and is responsible for 1% to 5% of all kinds of glomerulonephritides, and it accounts for 10% to 15% of crescentic glomerulonephritis.		
Global need from regulatory & scientific considerations	An GBM autoantibody IS would allow global harmonisation of unitage of GBM autoantibodies measured in patients predicted with the disease, improving patient care.		
ECBS outcome	[BLANK]		

Acute myeloid leukaemia

Proposal (title)	First WHO International Standard for measurable residual disease quantitation in acute myeloid leukaemia		
Proposer (name of Institution)	MHRA	**Principal contact**	Leandro Lo Cascio
Rationale	Disease recurrence is a major challenge in cancer care, affecting from 10% to over 70% of patients depending on the cancer type and stage. Traditional methods, such as imaging, often detect recurrence only at advanced stages, limiting therapeutic efficacy. Consequently, there is a critical need for earlier detection and more effective prediction of relapse. Measurable Residual Disease (MRD) testing is transforming cancer care by detecting subclinical disease levels post-treatment. This approach facilitates a paradigm shift from fixed regimens to precision-guided, response-adaptive therapies. In blood cancers, MRD status is a strong predictor of overall survival and is increasingly used to guide treatment decisions, reduce treatment-related toxicity. However, significant gaps in measurement, interpretation and standardisation limit the broader impact of MRD testing for patient care. Variable sensitivity, specificity and reproducibility across platforms and laboratories is leading to incomparable data and hindering establishment of analytical thresholds and clinical cutoffs. The field is largely unstandardised and the metrological means to ensure confidence in the measurements are currently lacking. To address this, in 2024 an expert advisory board was established through the NHS Chief Scientific Officer's Knowledge Transfer Partnership program to assess how molecular AML MRD testing could be further standardized. The expert advisory board identified the standardisation of molecular AML MRD testing as a critical priority, specifically for RUNX1::RUNX1T1, CBFB::MYH11 Type A, and NPM1 Type A (Scott et al., 2024). Building on the precedent set by the standardization of BCR::ABL1 in CML, we propose the development of a novel International Standard for high-accuracy molecular MRD quantification in haematological cancers, targeting sensitivity levels at or below current clinical thresholds (e.g. 10^{-3} to 10^{-5} mutant-to-reference gene ratio).		
Anticipated uses and users	The material is intended to serve as a primary standard for the calibration of diagnostic kits, assays, and secondary standards. The material will be validated for the detection of selected variants across a range of dilutions, traceable to the International Scale (IS), using qPCR, dPCR, and NGS platforms. The intended users include diagnostic laboratories and commercial manufacturers developing kits, assays, or secondary reference materials.		
Source/type of materials	Following the protocol established for the BCR-ABL1 WHO International Standard, we will screen AML cell lines to identify up to four clinically relevant genomic variants. A well-characterized wild-type control cell line will serve as the diluent to create a dilution series for each variant. The candidate materials, containing approximately $1.5x10^6$ lyophilized cells, with a targeted production of approximately 1,000 ampoules per dilution.		

Outline of proposed collaborative study	The collaborative study will allow assignment of fixed percent target/control gene values according to the International Scale for each variant, using techniques including qPCR, dPCR and NGS. Quantitative data derived from the collaborative study will be used to establish consensus values.		
Issues raised by the proposal	We gathered consensus support for the development of an AML MRD IS that could support the development of SI-traceable Reference Measurement Procedures and help regulatory decisions. Among others, NHS labs, UK NEQAS LI, LGC and commercial stakeholders. A European consortium of laboratories submitted an EURAMET proposal supporting this work.		
Action required	ECBS to endorse proposal.		
Proposer's project reference		**Date proposed:**	1 February 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	While molecular testing for targeted therapies for AML is globally approved, the diagnostic landscape for MRD remains fragmented. In the US, FDA approval is restricted to companion diagnostics for patient selection, with no authorised assays for longitudinal MRD monitoring. Conversely, the UK and EU offer limited CE-IVD marked options. Clinical practice predominantly relies on unstandardized Laboratory Developed Tests, which now face increasing regulatory pressure under the European IVDR transition.		
Number of products or methods	This material will support standardisation of all commonly used molecular assays, including qPCR, dPCR and NGS.		
Public health importance	With AML relapse rates reaching 70%, standardized MRD testing is a critical public health priority. It ensures equitable, accurate monitoring by eliminating dangerous laboratory variability. Validated standards enable precision medicine: preventing unnecessary toxicity, reducing healthcare costs, and detecting relapse early. This reliability is essential to improve global survival rates and ensure consistent, high-quality care for all patients.		
Global importance	Globally, inconsistent AML MRD testing hampers international clinical trials and drug development. A unified International Standard is essential to harmonize data across borders, accelerating access to life-saving therapies. By ensuring comparable results, we promote health equity, guaranteeing patients worldwide receive the same high accuracy monitoring regardless of location. This standardization is fundamental to improving survival outcomes and reducing the global burden of leukaemia.		
Global need from regulatory & scientific considerations	Scientifically, a unified standard is prerequisite for validating MRD as a surrogate endpoint in international clinical trials, ensuring data comparability across diverse platforms (NGS, dPCR). From a regulatory perspective, this metrological traceability is essential to harmonize FDA and IVDR compliance, enabling faster drug approvals. It bridges the gap between research and clinical utility, providing the robust framework needed for global precision oncology.		

ECBS outcome	[BLANK]

Circulating tumour DNA

Proposal (title)	First WHO International Standard for circulating tumour DNA		
Proposer (name of Institution)	MHRA	**Principal contact**	Abdalla Diaai Mohamed
Rationale	Liquid biopsy comprises a group of non-invasive tests that detect cancer-related analytes, such as circulating tumour DNA (ctDNA) in blood or other body fluids. ctDNA testing provides real-time information on tumour mutations, treatment response, and disease progression, offering a safer, repeatable alternative to traditional tissue biopsies for cancer monitoring and diagnosis. Precision medicine leverages molecular testing to identify specific genetic mutations that drive tumour development, enabling targeted therapies tailored to individual patients. Mutations in PIK3CA are frequently found in breast, colorectal, and endometrial cancers, guiding the use of PI3K inhibitors. NRAS and KRAS mutations are common in melanoma, colorectal, and non-small cell lung cancers (NSCLC), influencing treatment resistance and eligibility for certain inhibitors. BRAF mutations, particularly V600E, are significant in melanoma, thyroid, and colorectal cancers, with BRAF inhibitors offering substantial clinical benefit. TP53, a tumour suppressor gene, is mutated across a broad spectrum of cancers, including breast, lung, and ovarian, often associated with poor prognosis and guiding clinical trial enrolment. MAP2K1 mutations, affecting the MAPK pathway, are seen in melanoma and NSCLC, supporting the use of MEK inhibitors. Molecular profiling of these genes enables a more personalized and effective cancer treatment approach. There is a global public health need for accurate and sensitive cancer biomarker testing using technologies such as High-throughput sequencing (HTS; commonly referred to as next-generation sequencing) and digital PCR (dPCR). Crucially, this includes supporting the validation and verification of both laboratory-based sequencing and the bioinformatics data analysis involved in HTS workflows.		
Anticipated uses and users	This material is intended as a primary standard for the calibration of both clinically-actionable variants, and assay validation for many other oncogene variants in methodologies including dPCR and HTS. This material is also intended as non-assay-specific calibrant for assays or kits, of which several are commercially available, single target assays, small HTS panels and comprehensive HTS panels. Additionally, this material is intended to support validation and verification of bioinformatics pipelines involved in HTS workflow. Anticipated users are diagnostic laboratories and commercial entities developing kits, assays, or secondary standards.		
Source/type of materials	Fragmented DNA samples from up to 5 well-characterised cell lines (A375, HCT-15, HCT-116, MOLT4, NCI-H460) will be isolated and processed as previously described for the generation of the candidate WHO IS for EGFR variants ctDNA. The five DNA preparations from cancer cell lines will be mixed with DNA preparation from ATDB102 cell line (wild type) to obtain a final material containing seven clinically relevant genomic variants on multiple genes at a range of approximately 1-3% allelic frequency. The candidate material will		

	be diluted in DNA-depleted plasma and freeze-dried in approximately 1500 ampoules.		
Outline of proposed collaborative study	The collaborative study would evaluate the materials using a variety of diagnostic genotyping techniques, including dPCR and HTS. Quantitative data derived from the collaborative study would be used to establish consensus values for each of the materials, anticipated to include both percentage variant and total cfDNA quantity. Data from a commutability study on the candidate WHO IS for EGFR variants ctDNA, will be used to demonstrate the commutability of generated ctDNA with patients' samples.		
Issues raised by the proposal	ECBS previously endorsed a program to generate WHO international standards to support the development of HTS assays for BRAF variants (2016), PIK3CA variants (2018), multiple cancer biomarkers (2018), established the WHO 1st International standards for Cancer genomes (2019) and endorsed the proposed WHO 1st International standards for EGFR variants for ctDNA (2018). This proposal supports the need of international standards containing clinically actionable biomarkers at low Allele Frequency (AF%), extremely relevant for early diagnostics and post-treatment monitoring. HTS is an increasingly used diagnostic assay in the detection and quantification of multiple cancer mutations. The standards are proposed to be HTS-focused as the technique is currently unique in its parallel analysis of 1000's of relevant loci. However, there is much variation in platforms, wet lab components, and bioinformatics processing, all of which require validation, verification, and even calibration. The standard may also be appropriate for use in other single- and multi-analyte methods, such as RT-qPCR and dPCR. Additionally, this is intended to facilitate the alignment of liquid biopsy with solid tumour biopsy-based diagnostics as the cancer diagnostics community moves towards a non-invasive testing approach.		
Action required	ECBS to endorse proposal.		
Proposer's project reference		**Date proposed:**	1 February 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	Liquid biopsies are becoming predominant compared to conventional biopsies. ctDNA testing is expanding globally, including middle and low-income countries. CDx testing associated with precision medicine and post-treatment monitoring is becoming standards of care. There are already several commercially available HTS panels (Oncomine, Foundation One, Guardant 360) and often healthcare providers develop in-house solutions.		
Number of products or methods	This material will support standardisation of all commonly used molecular assays, including HTS.		
Public health importance	As recently reported in global cancer statistics 2022 report (GLOBOCAN), Cancer is a significant public health issue in the 21st century, with nearly 20 million new cases and 9.7 million deaths worldwide in 2022. New cancer cases are projected to reach 35 million by 2050. Investing in prevention and		

	diagnostics to target key risk factors could prevent millions of future diagnoses and save lives globally.
Global importance	Cancer is prevalent in all countries, with approximately 70% of cancer-related deaths occurring in low- and middle-income countries, where cancer incidence is rising most rapidly and access to early detection and treatment is limited. Accurate, sensitive ctDNA-based diagnostics in cancer patients will allow timely access to appropriate therapeutics. The emergence of biosimilar therapeutics will increase global access to cancer treatments, and thus the utility of diagnostic tests.
Global need from regulatory & scientific considerations	Accurate ctDNA genotyping is required to ensure patients receive a correct diagnosis, are matched to the optimal drug treatment, and are accurately monitored for treatment response and prognosis. International Standards will enable global standardisation of cancer genomic diagnostics to ensure a consistent, accurate, and safe approach.
ECBS outcome	[BLANK]

Antibodies to Oropouche virus

Proposal (title)	First WHO International Standard for antibodies to Oropouche virus		
Proposer (name of Institution)	MHRA	**Principal contact**	Yann Le Duff
Rationale	Oropouche virus (OROV) is a segmented single-stranded RNA virus belonging to the family *Peribunyaviridae,* one of the priority families listed in the WHO R&D Blueprint 2024 Pathogens Prioritization Framework. The virus is transmitted through the bite of midges or mosquitos. It is endemic in South America and Caribbean. OROV causes Oropouche fever, a usually mild to moderate disease, from which patients recover quickly. In some severe cases it may cause meningitis or encephalitis. However, since December 2023 there has been an evolution on this disease with increase in number of cases, severity, including 4 deaths (as of February 2025), vertical transmission and spread outside the endemic areas (https://www.paho.org/en/documents/epidemiological-alert-oropouche-region-americas-1-august-2024; Epidemiological Update Oropouche in the Americas Region - 11 February 2025 - PAHO/WHO | Pan American Health Organization). No specific treatment is available, and standard care is primarily focused on relieving symptoms. An R&D roadmap for Oropouche Medical Countermeasures has been drafted by the Collaborative Open Research Consortium (CORC) for Oropouche and was published on 5th January 2026 (https://cdn.who.int/media/docs/default-source/consultation-rdb/oropouche-roadmap.pdf?sfvrsn=726b3146_7&download=true). The 12 priorities for R&D include performing seroprevalence studies to assess population exposure, developing reagents and reference materials for assay development and advance therapeutic and vaccine candidates. The international standard for anti-OROV antibodies will be critical to support these priorities and ensure consistency and comparability across different clinical trials, facilitating the reliable evaluation of vaccine efficacy and potentially defining correlates of protection.		
Anticipated uses and users	Serological assays for assessment of antibodies responses to OROV infection, including seroepidemiologic studies, and vaccination (pre-clinical and clinical study). End users: clinical and public health laboratories, vaccine developers, assay kit manufacturer, research and/or control laboratories.		
Source/type of materials	Convalescent serum from 14 individuals with a confirmed exposure during the outbreaks in 2021- 2023 in Bolivia has been collected by Integrum Scientific supported by CEPI. Further convalescent serum/plasma from Panama is currently being sought as well.		
Outline of proposed collaborative study	Collaborative study will involve 10-20 laboratories worldwide, performing a range of serological assays for OROV, and representing control laboratories, manufacturers, clinical and academic laboratories.		
Issues raised by the proposal	None identified.		

Action required	ECBS to endorse proposal.		
Proposer's project reference		**Date proposed:**	1 February 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	There are currently no licenced vaccines and no specific therapeutics for OROV. Generic wide spectrum antivirals have been used in the clinic but there is a lack of evidence on their efficacy against OROV. Candidate vaccines are mainly in pre-clinical phase with a live attenuated OROV vaccine based on the strain BeAn 19991 being given to healthy individuals.		
Number of products or methods	Commercial assays include EUROIMMUN anti-Oropouche virus ELISA for IgM and IgG (https://www.euroimmun.com/oropouche-virus/). Most other methods detecting binding and neutralising antibodies are in-house.		
Public health importance	Since 2024, the number of Oropouche cases has increased, and the first deaths have been confirmed. This, combined with outbreaks in regions with a different climate (e.g. Cuba) from the endemic regions (Amazon area), has raised concern and increased awareness of this neglected disease.		
Global importance	WHO R&D Blueprint for Epidemics (https://www.who.int/publications/m/item/pathogens-prioritization-a-scientific-framework-for-epidemic-and-pandemic-research-preparedness), and UK Health Security Agency (Priority pathogen families research and development tool - GOV.UK) have all listed the *Peribunyaviridae* family as at high risk for pandemic potential and highlighted OROV as one of the prototype virus.		
Global need from regulatory & scientific considerations	Availability of a primary calibrant to harmonise results from serological assays is critical for accurate evaluation of treatments, including antibody therapies and vaccine, and for case management and surveillance.		
ECBS outcome	[BLANK]		

Meningococcal serogroup X polysaccharide

Proposal (title)	Second WHO International Standard for meningococcal serogroup X polysaccharide		
Proposer (name of Institution)	MHRA	**Principal contact**	Sharon Tierney
Rationale	The 1st International Standard (IS) for Meningococcal Group X Polysaccharide (MenX PS) (code 14/156) is a freeze-dried preparation containing 0.776 ± 0.089 mg of MenX PS per ampoule, as determined by quantitative nuclear magnetic resonance (qNMR) spectrometry. Stocks of the 1st IS are now running low and a replacement standard is therefore needed.		
Anticipated uses and users	The standard is primarily used by vaccine manufacturers and national control laboratories to calibrate in-house reference standards or as a working standard in assays that quantify MenX PS in final vaccine products or bulk components. It is also used as a coating antigen in ELISA to measure immune responses against MenX. Approximately 70 ampoules of the 1st IS are distributed each year.		
Source/type of materials	Purified MenX PS has been donated by a vaccine manufacturer for production of a candidate standard. A batch of approximately 3,000 ampoules, each containing ~1 mg of PS, will be produced.		
Outline of proposed collaborative study	The collaborative study will be similar to that done for the 1st IS (Vipond *et al.*, 2015, WHO/BS/2015.2255). PS content will be assigned by qNMR, using a spectral standard and protocol provided by the MHRA. Participants will also be asked to perform fitness for purpose methods such as the phosphorus assay, HPAEC-PAD and rate nephelometry.		
Issues raised by the proposal	None.		
Action required	ECBS to endorse proposal.		
Proposer's project reference		**Date proposed:**	1 February 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	A pentavalent conjugate vaccine covering serogroups ACYWX has been prequalified by WHO and is licensed in India.		
Number of products or methods	Although there is currently only one product on the market, it is likely that this will be more widely licensed in future.		

Public health importance	MenX vaccines are an important preventative strategy to control MenX disease. The IS for MenX PS supports quality control during manufacturing and is critical for regulatory approval of new MenX vaccines. It is important that MenX content, or potency, in monovalent and multivalent meningococcal conjugate vaccines is accurately determined. Excess MenX PS could result in a vaccine that dominates the immune response and potentially impacting immune responses to other active components. Insufficient MenX PS could result in a vaccine that lacks protective efficacy.
Global importance	Serogroup X meningococci has emerged as an important pathogen, causing outbreaks in parts of sub-Saharan Africa, particularly within a region known as the meningitis belt. Vaccines against MenA, C, W and Y have proven effective in preventing disease. There is a clear need for MenX PS and conjugate vaccines to prevent further MenX outbreaks.
Global need from regulatory & scientific considerations	Previously, the PS content of glycoconjugate vaccines has been determined using a variety of methods and standards. These standards were often PS derivatives and therefore not directly comparable to the vaccine material being measured. As MenX is relatively new, the manufacturing and testing of X-containing vaccines is challenging. Ensuring the continuity of the MenX PS IS will improve the harmonisation of quantitative MenX assays used in vaccine quality control and further support the development of MenX PS and conjugate vaccines.
ECBS outcome	[BLANK]

Antibodies to human immunodeficiency virus

Proposal (title)	Second WHO International Reference Panel for antibodies to human immunodeficiency virus		
Proposer (name of Institution)	MHRA	**Principal contact**	Manasi Majumdar
Rationale	The first WHO HIV (antibody) International Reference Panel was established by WHO in 2006. It is used by manufacturers, Research Institutes and Health Care authorities to compare the sensitivity and specificity of a range of assays able to detect antibodies to HIV. Current stocks are close to exhaustion and a replacement panel will be needed within the next 3 years.		
Anticipated uses and users	Used to demonstrate that specific assays can detect the different HIV subtypes. Users will be manufacturers, health care professional, research institutes.		
Source/type of materials	6 Solvent-detergent treated human plasma containing antibodies to HIV (the same source material used to make the 1st IRP will be used to make the replacement IRP) diluted in normal human serum. Each panel will contain: anti-HIV-1 subtype A (Group M) anti-HIV-1 subtype B (Group M) anti-HIV-1 subtype C (Group M) anti-HIV-1 subtype E (Group M) anti-HIV-1 Group O anti-HIV-2		
Outline of proposed collaborative study	A collaborative study of up to 20 participants from commercial, health care and research institutes will be conducted to demonstrate fitness for purpose of the proposed replacement panel in relevant analytical methods.		
Issues raised by the proposal	None.		
Action required	ECBS to endorse proposal.		
Proposer's project reference		**Date proposed:**	1 February 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	N/A		

Number of products or methods	Methods that will be assessed will be commercially based CLIA, ELISA and Point of Care tests. This panel can also be used to assess in-house assays used for research purposes.
Public health importance	High. This panel is used to show that assays can successfully detect multiple subtypes of HIV-1 and HIV-2.
Global importance	High. The subtypes in the panel represent global subtypes.
Global need from regulatory & scientific considerations	It is essential that assays are able to detect these HIV subtypes.
ECBS outcome	[BLANK]

Granulocyte colony stimulating factor (G-CSF)

Proposal (title)	Third WHO International Standard for granulocyte colony stimulating factor (G-CSF)		
Proposer (name of Institution)	MHRA	**Principal contact**	Kata Dix
Rationale	The current 2nd WHO International Standard (IS) for Granulocyte colony stimulating factor (G-CSF, NIBSC code 09/136) has been available since 2010. This standard is used globally for the potency assignment of well-established G-CSF therapeutic products and their biosimilars. In the 15 years since its establishment, between 200 and 250 ampoules/year of 09/136 are dispatched and it has now depleted to a level where replacement will be needed.		
Anticipated uses and users	Intended for the calibration of G-CSF based therapeutic products.		
Source/type of materials	Two lyophilized candidates: 08/350 and 09/160, (both *E. coli* – derived) from the previous collaborative study (WHO/BS/10.2133) to establish the 2nd IS for G-CSF are stored and can be used as candidates for the 3rd IS. Accelerated thermal degradation study samples are available for both candidates. Stability assessments will be performed and new material will be sourced in case the available ones are not found suitable.		
Outline of proposed collaborative study	The currently available candidates were included in the collaborative study for the establishment of the 2nd IS 09/136 (WHO/BS/10.2133). In this study, data from 13 different laboratories were used to assign potency values relative to the 1st WHO IS, 88/502. In addition, potencies for all candidates were re-calculated relative to the 2nd WHO IS 09/136. All laboratories used bioassays based on cell proliferation, and one participant also submitted results from a reporter gene assay. The cell lines used for the cell proliferation assays were representative of those described in current versions of the Japanese, Chinese, European and US Pharmacopoeias, therefore we propose that the potency value calculated in this study, relative to the 2nd WHO IS 09/136, is assigned to a candidate if found suitable in the stability studies. A collaborative study of similar size (up to 15 - 20 laboratories) will be organized, should the preparation of new candidates become necessary.		
Issues raised by the proposal	No issues raised. Most available G-CSF therapeutics and both candidates are expressed in *E. coli.*		
Action required	ECBS to endorse proposal.		
Proposer's project reference		**Date proposed:**	1 February 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			

Approval status of medicine or in vitro diagnostic method	Several filgrastim biosimilars are already authorised for use worldwide, and additional G-CSF analogue biologics have been approved. For the harmonisation of PEG-G-CSF products, a separate WHO IS has been established. Cellular assay methods for the potency calibration of these products are well established and are included in pharmacopoeias. They are based on the proliferation of G-CSF sensitive cell lines (NFS-60, M-NFS-60, 32D cells).
Number of products or methods	Several G-CSF products have marketing authorisations globally and novel long-acting analogues, as well as biosimilars are being developed.
Public health importance	Based on their mechanism of action stimulating the production and release of neutrophil granulocytes from the bone marrow, G-CSF based therapeutics are authorised for uses including reducing the incidence of febrile neutropenia in patients receiving cytotoxic chemotherapy, reducing the duration of neutropenia after bone marrow destruction as part of pre-transplant treatment, decreasing the risk of infection in patients with neutropenia or advanced HIV infection, and to mobilise neutrophils in healthy individuals in advance of stem cell donation.
Global importance	The current 2nd WHO IS for G-CSF (09/136) is used worldwide. Compendial standards calibrated to the IS are also available locally.
Global need from regulatory & scientific considerations	This is a replacement standard for the bioactivity calibration of therapeutic products that are distributed all over the world.
ECBS outcome	[BLANK]