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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 12 – 15 October 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 **25 September 2026** and should be addressed to:

Biologicals Norms and Standards and Transplantation
Product Standards, Specifications and Nomenclature
Department of Medicines and Health Products Policies and Standards
World Health Organization
1211 Geneva 27
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Comments should be submitted electronically to **Dr Ivana Knezevic** at email:
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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. First WHO International Reference Preparation for Anti-yellow fever serum
2. First WHO International Standard for antibodies to Hantavirus
3. Second WHO International Standard for antibodies to SARS-CoV-2 VOC
4. First International Standard for antibodies to Bundibugyo virus
5. First WHO International Standard for antibodies to Klebsiella pneumoniae
6. First WHO International Standard for human herpes virus 8 DNA for NAT
7. WHO International Reference Reagent for anti-D serological reactivity
8. Seventh WHO International Standard for Haemoglobincyanide
9. Second WHO International Standard for Interleukin-1β
10. Third WHO International Standard for Molecular weight calibration of low molecular weight heparin

Anti-Yellow Fever Serum

Proposal (title) including anticipated WHO IBRS category	Proposal to replace the WHO International Reference Preparation for Anti-Yellow Fever Serum		
Proposer (name of Institution)	NIBSC/MHRA	**Principal contact**	Paul Stickings
Rationale	WHO established an International Reference Preparation for Anti-Yellow Fever Serum, Monkey in 1962 (NIBSC code: YF). The intended use for this reference preparation was to as a positive control serum in the mouse protection test used in the control of yellow fever vaccine. This preparation was also assigned a potency value in IU because it was also found to be useful for yellow fever neutralisation assays. Stocks of YF monkey serum are now close to exhaustion YF has been used by vaccine manufacturers who need to conduct immunogenicity assays in NHPs for new virus master and working seeds (Annex 5, TRS 978, 2013) and by vaccine manufacturers / developers and other laboratories who are performing YFV neutralisation assays for human serum samples obtained from clinical trials or conducting research and surveillance into YFV immunity in different populations. We propose the development of two reference preparations to replace YF: a like-for-like monkey serum standard, intended to be used for assay of NHP immune serum and a human immune serum, intended to be used for assay of human samples. The provision of a human serum standard is likely to be more suitable for assays of human serum samples and will reduce the need for shipment of monkey serum (for which specific export/import permits are required) to users who do not need to use a monkey serum		
Anticipated uses and users	Laboratories developing and/or performing assays that are used to measure antibodies to yellow fever virus. This is likely to include yellow fever vaccine manufacturers and developers, national control and public health laboratories and academic labs		
Source/type of materials	Monkey immune serum to be obtained from a yellow fever vaccine manufacturer Human immune serum to be obtained from blood collected from individuals in a region where yellow fever vaccine coverage is high		
Outline of proposed collaborative study	Laboratories who are experienced with performing neutralisation assays for YFV will be invited to participate in the collaborative study. A small panel of human serum samples representing vaccine-induced and natural-infection-induced immunity from different regions will be included for an assessment of commutability		
Issues raised by the proposal	The status (e.g. WHO IS vs. WHO RR) and the approach to value assignment for the proposed candidate standards will require further thought as the project develops		

Proposer's project reference	SLP0094	**Date proposed**	July 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (Recommendations for the preparation, characterization, establishment and use of WHO international biological reference standards. 2026)			
Approval status of medicinal product or in vitro diagnostic method that the IBRS is intended for; and the number of products (or diagnostic assays) that are in use	Yellow fever vaccines are licensed in multiple countries worldwide and some products have been pre-qualified by WHO; neutralisation assays are the cornerstone of clinical trial evaluation because efficacy studies are not feasible. There are a number of commercial immunoassay kits for measuring yellow fever antibodies (IgM or IgG) on the market. In-house developed tests are also used. However, it is not yet known if we will include binding assays in the collaborative study		
Public health importance and global need for the IBRS from a regulatory and scientific perspective	Current standard is referenced in WHO TRS for yellow fever vaccines. Many countries in Africa and Latin America are classified as high-risk for yellow fever outbreaks. The potential for international spread to unaffected regions remains a global health security concern. An estimated 67 000–173 000 severe infections and 31 000–82 000 deaths occur each year in Africa and the Americas [Gaythorpe KA et. al. The global burden of yellow fever. Elife. 2021]		

Antibodies to Hantaviruses

Proposal (title) including anticipated WHO IBRS category	The First WHO International Standard for antibodies to Hantaviruses		
Proposer (name of Institution)	NIBSC/MHRA	**Principal contact**	Yann Le Duff
Rationale	Hantaviruses are a family of zoonotic viruses which infect mainly rodents and are occasionally transmitted to humans. There are two types of diseases associated with hantavirus infection: hantavirus cardiopulmonary syndrome (HCPS), a rapidly progressive condition affecting the lungs and heart, and haemorrhagic fever with renal syndrome (HFRS), which primarily affects the kidneys and blood vessels. Although many hantavirus species have been identified worldwide, only a limited number are known to cause human disease. Old World Hantaviruses found in Europe (e.g. Puumala virus) and in East Asia (e.g. Hantaan virus) cause HFRS. New World Hantaviruses from North, Central and South America (e.g. Andes virus, Sin Nombre virus) are known to cause HCPS. The Andes virus is the only hantavirus for which human-to-human transmission has been documented among close and prolonged contacts, primarily in Argentina and Chile, and in April-May 2026 in the MV Hondius cruise. There is currently only one vaccine (Hantavax) licensed in South Korea, but with very limited use, and several candidates are in development. To support the development and evaluation of vaccines and diagnostics, a WHO International Standard for antibodies will be required. Expressing results of these studies in the same WHO IS unitage will facilitate comparability and contribute to the identification of possible correlates of protection for vaccine assessment. We aim to generate a WHO IS to be used as calibrant for both binding and neutralisation assays.		
Anticipated uses and users	The standard will be used in serological assays for assessment of antibody responses to Hantavirus infection, including seroepidemiologic studies, and vaccination (pre-clinical and clinical study). End users: clinical and public health laboratories, vaccine developers, assay kit manufacturers, research laboratories.		
Source/type of materials	Through CEPI, two donor organisations have been identified based in Bolivia and Panama. They will provide convalescent plasma/sera from individuals recovered from New World Hantavirus in Bolivia (presumed Andes virus) and Panama (confirmed Choclo virus, known to cross react with Andes virus). We will also aim to source material from other regions including Europe and East Asia from individuals exposed to Old World Hantavirus in order to evaluate cross reactivity.		

Outline of proposed collaborative study	The collaborative study will involve 15-20 laboratories worldwide, performing a range of serological assays for anti-Hantavirus antibodies. We will aim to include laboratories using different species of Hantaviruses to understand cross reactivity. Based on the results of the study, the name of the standard may need to be reviewed to make it more specific (e.g. WHO IS for antibodies to Andes virus).		
Issues raised by the proposal	With limited information on cross reactivity, it is important to source samples from individuals exposed to different Hantaviruses, even within the Old World and New World subgroups. Therefore, it is currently unclear whether one WHO Internation Standard for Hantaviruses will be suitable or if virus specific standards will be needed.		
Proposer's project reference		**Date proposed**	30 June 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (Recommendations for the preparation, characterization, establishment and use of WHO international biological reference standards. 2026)			
Approval status of medicinal product or in vitro diagnostic method that the IBRS is intended for; and the number of products (or diagnostic assays) that are in use	There is currently only one vaccine licensed in South Korea, but with very limited use, and no specific therapeutics for hantavirus infections. Some generic wide spectrum antivirals have demonstrated efficacy: Favipiravir (RdRp inhibitor) potentially as PEP and Ribavirin (but no effect post infection). 2 DNA vaccines developed by USAMRIID have completed phase I CT; 1 MVA- based vaccine is being evaluated in phase I CT; several candidates are in early or preclinical development. They incorporate one or more antigens from Hantaviridae, most of them targeting Andes, Sin Nombre, Puumala and Hantaan viruses. The antigens are mainly the glycoprotein Gn, Gc or precursor GPC, but also nucleoprotein in some cases.		
Public health importance and global need for the IBRS from a regulatory and scientific perspective	Hantaviruses can cause severe and potentially fatal diseases and medical countermeasures are needed for epidemic preparedness. This has been highlighted by the Andes virus outbreak linked to a cruise ship, where rare human-to-human transmission was recorded, further highlights the urgent need to better understand viral spread, outbreak preparedness, and global response measures. WHO R&D Blueprint for Epidemics (https://www.who.int/publications/m/item/pathogens-prioritization-a-scientific-framework-for-epidemic-and-pandemic-research-preparedness), UK Health Security Agency (Priority pathogen families research and development tool - GOV.UK) and UK Vaccine Network (UK Vaccine Network - GOV.UK) have all listed the Hantaviridae family as at high risk for pandemic potential. Availability of a primary calibrant to harmonise results from serological assays is critical for accurate evaluation of		

	countermeasures, including antibody therapies and vaccines, but also for diagnostics, patient management and surveillance.

Antibodies to SARS-CoV-2

Proposal (title) including anticipated WHO IBRS category	Second WHO International Standard for antibodies to SARS-CoV-2 variants of concern		
Proposer (name of Institution)	NIBSC/MHRA	**Principal contact**	Giada Mattiuzzo
Rationale	In 2022, ECBS established the First WHO International Standard (IS) for antibodies to SARS-CoV-2 variants of concern (VOC) (NIBSC code 21/338). The intended use of this standard was for neutralisation assays when testing VOC of Omicron lineage or newly emerging variants, to complement the existing replacement (2nd) WHO IS for anti-SARS-CoV-2 antibodies (21/340). The standard was deemed necessary due to the lack of neutralising activity of 21/340 against emerging VOC, Omicron lineage. Interestingly, 21/338 does not include plasma from individuals exposed to Omicron; however, cross-reactivity against Omicron and subsequent VOC is likely conferred by the large pool of donations from vaccinated and previously infected individuals (>250 donors). From the end of 2022 to May 2026, 917 units have been distributed worldwide. Following an initial peak in demand in 2023 (570 units), distribution stabilized in 2024 and 2025 at approximately 100 ampoules per year. In 2026, there has been a marked decline in demand (11 units distributed over five months). In addition, customers have raised questions regarding the potency of this standard against newer SARS-CoV-2 VOC, some of which are included in updated vaccine formulations. Our analysis confirms that the potency of 21/338 against some recent VOC is insufficient for use as a primary calibrant, as it does not support an adequate dilution series: **Variant IC50 (21/338)** VIC01 22894.8 BA.1 1469.6 BA.2 1875.2 BA.4 1152.8 BA.5 769.2 BA.2.75.3 989.6 BA.4.6 610.9 BA.2.75.2 115.5 BQ.1.22 123.5		

	XBB.1.1 80.6 XBB.1.5 73.5 CH.1.1 49.9 XBB.1.16 105.8 EG.5.1.1 64.3 JN.1 73.1 BA.2.86 113.1 We therefore propose replacing the current standard with a new version that is suitable to serve as a WHO International Standard, to continue supporting the evaluation of immunological responses elicited by infection and vaccination.
Anticipated uses and users	In serological assays to compare results between laboratories using the same SARS-CoV-2 variants; for the evaluation of immunological responses to new isolates; for the evaluation of antibody responses elicited by new vaccines/new versions of licensed vaccines; and in sero-epidemiological studies.
Source/type of materials	Plasma donations from UK population or other regions collected from 2020 until 2026 will be screened and selected based on high neutralising antibody titres against many SARS-CoV-2 variants. Similar to the strategy used to formulate 21/338 we aim to pool together donations from a large number of individuals who have been vaccinated and infected with different SARS-CoV-2 variants for a broader specificity.
Outline of proposed collaborative study	The collaborative study will involve about 15-20 laboratories worldwide, performing a range of serological assays for SARS-CoV-2 antibodies, with a focus on neutralisation assays using different variants. The aims will be to assess the suitability of the candidate replacement to serve as reference material for serological assays for SARS-CoV-2 • characterisation of the antibody preparations in terms of reactivity/specificity in different assay systems; this will also include performance against different variants • evaluate performance of the replacement IS in parallel to the current First WHO IS for antibodies to SARS-CoV-2 variants • propose an appropriate unitage to assure continuity between the first and second IS against the early 2020 isolate. No variant-specific unitage will be assigned as it is currently done for 21/338.
Issues raised by the proposal	None identified

Proposer's project reference		**Date proposed**	29 June 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (Recommendations for the preparation, characterization, establishment and use of WHO international biological reference standards. 2026)			
Approval status of medicinal product or in vitro diagnostic method that the IBRS is intended for; and the number of products (or diagnostic assays) that are in use	Several vaccines were developed and authorised during COVID-19 pandemic. Currently 5 are authorised by EMA in Europe (COVID-19 medicines | European Medicines Agency (EMA) and 4 by FDA in USA. These include mRNA vaccines and a subunit vaccine. The WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) advises manufacturers that monovalent JN.1 or KP.2 vaccines remain appropriate vaccine antigens; monovalent LP.8.1 is a suitable alternative vaccine antigen. The 2025–2026 formulations for COVID-19 vaccines in the United States are based on the Omicron JN.1-lineage of SARS-CoV-2: i.e., Moderna and Pfizer-BioNTech (LP.8.1 strain), and Novavax (JN.1 strain) (Overview of COVID-19 Vaccines and Vaccination | Covid | CDC). There are many kits in the marker to measure antibody responses to SARS-CoV-2. For neutralisation assays, there are surrogate assays which have the same format of an ELISA but target epitopes which correlate well with neutralisation activity. It is however unclear how well these commercial kits have updated to the new variants. In-house methods using SARS-CoV-2 or alternative system (e.g. pseudotyped virus) are still widely used and can adapt quickly to new emerging variants		
Public health importance and global need for the IBRS from a regulatory and scientific perspective	While the public health importance of COVID-19 is no longer as acute as in 2020–2022, it remains significant. SARS-CoV-2 continues to circulate worldwide and, particularly among older individuals, immunocompromised populations, or those with underlying medical conditions, infection can still lead to severe disease and death. In addition, long COVID remains a major concern, with persistent symptoms impacting the workforce and having economic consequences. Vaccination remains the most effective tool to minimise disease severity. However, vaccines may require updating as new variants emerge, which could affect the level of protection conferred by current formulations.		

Antibodies to Bundibugyo virus

Proposal (title) including anticipated WHO IBRS category	First WHO International Standard for antibodies to Bundibugyo virus		
Proposer (name of Institution)	NIBSC/MHRA	**Principal contact**	Giada Mattiuzzo
Rationale	*Filoviridae* is a family of viruses causing haemorrhagic fever and is listed by the WHO R&D Blueprint as being at high risk for epidemics. There are six species within the genus *Orthoebolavirus*. WHO International Standards for antibodies to the two species with the highest incidence and case-fatality rate, Ebola virus and Sudan virus, were previously established by ECBS in 2017 and 2025 respectively. On 17th May 2026, WHO declared the outbreak of Bundibugyo virus disease in the Democratic Republic of Congo (DRC) and Uganda, caused by another species, Bundibugyo virus (BDBV), a Public Health Emergency of International Concern (PHEIC). As of 24 June 2026, there have been over 1000 confirmed cases and 293 deaths in DRC and Uganda and 1 DRC-exported case in France (https://www.ecdc.europa.eu/en/ebola-outbreak-democratic-republic-congo-and-uganda). Previously, there have only been two recorded outbreaks of BDBV: in Uganda in 2007 (149 cases, 25% fatality rate) and in DRC in 2012 (57 cases, 51% fatality rate). There are currently no approved vaccines or specific therapeutics for BDBV. Cross-protection from licensed Ebola virus vaccines remains unclear based on pre-clinical data. An evidence map summarising all of the publications on BDBV is available: https://livingevidence.org.au/research-initiatives/about-feeva/evidence-maps/ Several vaccines are in development, and the availability of a WHO International Standard for antibodies will support their evaluation as well as enable comparison of the results from clinical studies.		
Anticipated uses and users	Development and calibration of serological assays (e.g. ELISA, neutralisation assays) for identification and/or potency testing of anti-BDBV antibodies in: • clinical and public health laboratories • vaccine manufacturers - Vaccine studies • therapeutic antibody producers • assay kit manufacturers • research laboratories		
Source/type of materials	Donated human plasma or serum from convalescent individuals. With the support of CEPI we are contacting partners in DRC and Uganda to assess availability of such material. Vaccinees' serum could also be sourced to act as a comparator during the collaborative study.		

Outline of proposed collaborative study	The collaborative study will involve 10-20 laboratories worldwide, performing a range of serological assays for BDBV, and representing control laboratories, manufacturers, clinical and academic laboratories. The aim will be to assess the suitability of different antibody preparations to serve as the international standard with an assigned unitage per mL for use in the harmonisation of BDBV serology assays by: • characterising the antibody preparations in terms of reactivity/specificity in different assay systems • assessing each preparation's potency i.e. readout in a range of typical assays performed in different laboratories • assessing commutability i.e. establishing the extent to which each preparation is suitable to serve as an interim standard for the variety of different samples and assay types.		
Issues raised by the proposal	Logistics: Sourcing material from endemic regions could be challenging, especially during a PHEIC and setting up material transfer agreement may take time Biosafety and Biosecurity: BDBV is a schedule 5 and BSL4 agent. Previously approved SOPs for reception and handling of Ebola virus antibody material will be followed for material donated by individuals infected with BDBV.		
Proposer's project reference		**Date proposed**	29 June 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (Recommendations for the preparation, characterization, establishment and use of WHO international biological reference standards. 2026)			
Approval status of medicinal product or in vitro diagnostic method that the IBRS is intended for; and the number of products (or diagnostic assays) that are in use	There are not licensed vaccines or specific therapeutics for BDBV. Repurposed antivirals Remdesivir and Obeldesivir have demonstrated efficacy in NHP for Ebola virus and Marburg virus. Monoclonal antibodies cocktails or combination therapy with antivirals have shown encouraging results. Several vaccines are in development, specific for BDBV or in combination with other antigens from other *Orthoebolavirus spp.* CEPI is currently funding IAVI, Moderna, Oxford University and PHV (CEPI fast-tracks three Bundibugyo ebolavirus vacchttps://cepi.net/cepi-fast-tracks-three-bundibugyo-ebolavirus-vaccine-candidatesine candidates and https://cepi.net/cepi-awards-public-health-vaccines-us19m-accelerate-bundibugyo-ebolavirus-vaccine) Majority of methods are in-house assays. Some commercial ELISAs are available for research use only: • Creative Diagnostics, Assy Genie and Alpha Diagnostics- against GP • RayBiotech against VP24.		

	• One pan-filovirus multiplex assay from Tetracore- manufacturer specified that the assay specificity includes antibodies against BDBV.
Public health importance and global need for the IBRS from a regulatory and scientific perspective	As of 17th May 2026, BDBV outbreak in DRC and Uganda has been declared a PHEIC. Availability of a primary calibrant to harmonise results from serological assays is critical for accurate evaluation of treatments, including antibody therapies and vaccines, and for case management and surveillance. A research reagent will be prepared to bridge until an IS is available and it will be added to the collaborative study for calibration.

Antibodies to *Klebsiella pneumoniae*

Proposal (title) including anticipated WHO IBRS category	First WHO International Standard for Antibodies to *Klebsiella pneumoniae*		
Proposer (name of Institution)	MHRA/NIBSC	**Principal contact**	Arif Felek
Rationale	*Klebsiella pneumoniae* is a major antimicrobial-resistant (AMR) pathogen and an important cause of neonatal sepsis and hospital-acquired infections, including pneumonia. The pathogen has been identified as a top-priority bacterial pathogen by the World Health Organization, highlighting the urgent need for preventive strategies, including vaccines. Several vaccine candidates targeting capsular (K) and lipopolysaccharide (O) antigens of *K. pneumoniae* are currently under development. However, there is currently no international antibody standard available to support the development, validation, and comparison of immunological assays used to evaluate vaccine-induced immune responses. The absence of standardized reagents limits the ability to: • Harmonise immunoassays across laboratories • Compare immune responses between vaccine candidates • Establish correlates of protection To address this gap, MHRA/NIBSC proposes developing the first WHO International Standard for antibodies to Klebsiella pneumoniae. The proposed material will consist of a human hyperimmune intravenous immunoglobulin (hIVIG) preparation containing antibodies to clinically relevant *K. pneumoniae* antigens donated by the University of Maryland, Baltimore (UMB). This material may be blended with convalescent serum samples collected by Wits VIDA (University of the Witwatersrand) to increase serotype coverage, provided that these samples contain sufficient antibody levels. Once established, the standard will serve as a calibration reference for immunoassays, enabling antibody responses to be expressed in International Units (IU) and improving the comparability of results across laboratories and clinical studies.		
Anticipated uses and users	The proposed International Standard will support: • Standardisation of ELISA and multiplex immunoassays measuring antibodies to K. pneumoniae polysaccharide antigens • Calibration of functional antibody assays, including opsonophagocytic killing assays • Harmonisation of immunogenicity data generated during clinical development of Klebsiella vaccines		

	Potential users include: • Vaccine developers and manufacturers • Academic research laboratories • Regulatory laboratories • Contract research organisations performing immunogenicity testing		
Source/type of materials	Pooled human hyperimmune serum (University of Maryland, Baltimore) High-titre convalescent sera from the University of the Witwatersrand-Vaccines and Infectious Diseases Analytics (VIDA).		
Outline of proposed collaborative study	A multi-laboratory collaborative study will be conducted to evaluate the candidate International Standard. Participating laboratories can include academic institutions, vaccine developers, and reference laboratories with expertise in Klebsiella immunology. The study will evaluate the candidate standard across multiple assay platforms, including: • Enzyme-linked immunosorbent assays (ELISA) • Multiplex bead-based immunoassays Participants will measure antibody responses to relevant Klebsiella antigens using the candidate serum preparation and a panel of test samples. The study aims to: • Assess the inter-laboratory reproducibility of antibody measurements • Establish consensus estimates of antibody activity • Assign International Units (IU) for antibody levels Results will be analysed at MHRA/NIBSC and compiled into a report submitted to the WHO Expert Committee on Biological Standardisation (ECBS).		
Issues raised by the proposal	• Antigenic diversity of Klebsiella pneumoniae, which may influence assay specificity • Differences in immunoassay platforms used across laboratories		
Proposer's project reference	SLP0084	**Date proposed**	16/07/2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (Recommendations for the preparation, characterization, establishment and use of WHO international biological reference standards. 2026)			
Approval status of medicinal product or in vitro diagnostic method that the IBRS is intended for; and the number of products (or	No licensed vaccines for *Klebsiella pneumoniae* currently exist. Multiple candidates are in pre-clinical and clinical development.		

diagnostic assays) that are in use	
Public health importance and global need for the IBRS from a regulatory and scientific perspective	Klebsiella pneumoniae is a major antimicrobial-resistant (AMR) pathogen and an important cause of neonatal sepsis and hospital-acquired infections with significant associated morbidity and mortality. The pathogen is widely distributed globally and is recognised as a priority pathogen for the development of new preventive strategies.

Human herpesvirus 8 DNA for NAT tests

Proposal (title) including anticipated WHO IBRS category	First WHO International Standard for human herpesvirus 8 DNA for nucleic acid amplification technology-based tests		
Proposer (name of Institution)	NIBSC (MHRA)	**Principal contact**	Jacqueline Fryer
Rationale	Human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), is an oncogenic herpesvirus that establishes lifelong latency in B cells following primary infection. Transmission occurs predominantly via saliva, although sexual contact, intravenous drug use, blood transfusion, and solid organ transplantation (SOT) are also recognised routes. HHV-8 infection is typically asymptomatic in immunocompetent individuals but is causally associated with several disorders in immunocompromised patients, including Kaposi's sarcoma, primary effusion lymphoma, multicentric Castleman's disease, and KSHV inflammatory cytokine syndrome (KICS). In transplant recipients, HHV-8 infection may arise from reactivation of latent virus in the recipient or primary infection following transmission from the donor. Donor-derived primary HHV-8 infection is associated with high viral loads, increased risk of all HHV-8-related disease manifestations, and poor clinical outcomes. Although HHV-8-associated disease has long been recognised in people living with HIV, it remains infrequently reported in solid organ transplant recipients (SOTR). This likely reflects diagnostic limitations, under-recognition of disease (particularly KICS), and incomplete case ascertainment. Unlike other human herpesviruses, HHV-8 is not ubiquitous. Seroprevalence is generally <10% in Northern Europe, Asia, and the United States, compared with >50% across much of sub-Saharan Africa [1]. Intermediate seroprevalence rates (10–30%) are observed in Mediterranean countries. The importance of early detection and accurate monitoring of HHV-8 DNA using nucleic acid amplification technology (NAT)-based assays is increasingly recognised for risk assessment and disease management in transplant recipients. Detection of HHV-8 DNAemia in high-risk SOTR enables timely interventions, including reduction or modification of immunosuppression (e.g., conversion to mTOR inhibitors), antiviral therapy, and rituximab treatment, which may improve clinical outcomes. Donor screening is also increasingly recommended to identify recipients at risk of HHV-8-associated disease and to guide post-transplant virological monitoring [2,3]. In the UK, universal HHV-8 screening of deceased organ donors was introduced in 2023. Initial screening strategies relied on serology; however, emerging evidence supporting the utility of HHV-8 DNA detection has highlighted the value of combining NAT and serological testing to reduce the risk of donor-derived transmission [4].		

	Both commercial and laboratory-developed NAT assays are available for HHV-8 detection. Data from the 2025 INSTAND external quality assessment (EQA) programme for HHV-8 genome detection showed that 40% of participating laboratories performed quantitative testing and 60% qualitative testing, with commercial and laboratory-developed assays used with similar frequency [5]. Establishment of a WHO International Standard for HHV-8 DNA would support the development, validation, and standardisation of NAT-based assays for donor screening and the management of HHV-8 infection in immunocompromised patients. Such a standard would facilitate comparison of assay performance across platforms and laboratories and support the development of evidence-based clinical guidelines for HHV-8, ultimately contributing to improved patient outcomes.
Anticipated uses and users	A WHO International Standard for HHV-8 DNA would support the calibration of NAT-based tests. Use of a common unit for measurement of HHV-8 DNA would enable the comparison of results from different tests and support the establishment of clinical practice guidelines with the aim of improving patient outcomes. The anticipated users are clinical laboratories, in-vitro diagnostics (IVD) manufacturers, clinical and reference laboratories and external quality assessment (EQA) providers. The NIBSC catalogue includes a number of WHO International Standards which support the use of NAT in the management of related herpesvirus infections in transplant patients. Sales of these materials range from ~40 to 250/year but based on the lower incidence of HHV-8 infection in transplant patients it is anticipated that sales for a standard for HHV-8 DNA would likely be at the lower end of this range.
Source/type of materials	The proposed HHV-8 source material is whole virus cultured from B cell lines known to carry HHV-8 (but negative for other herpesviruses such as EBV). Various cell lines containing HHV-8 are available from national cell culture collections. Virus derived from cell culture has been determined to be a suitable source material for related WHO reference materials for NAT (i.e. the WHO International Standards for HCMV, EBV, VZV, HSV and HHV6 DNA). For these materials it was not feasible to source material from patient samples because of the low volumes of material available from transplant patients and the transient nature of herpesvirus DNA in patients undergoing treatment. Inactivation of source materials has yet to be determined. Heat treatment has been used to inactivate ACDP3 source materials (SARS RNA, HIV RNA) without impacting downstream NAT applications but has not been performed historically for related herpesvirus WHO reference materials for NAT.
Outline of proposed collaborative study	The collaborative study would likely follow a typical study design for a 1st WHO International Standard with the principal aim of assigning the candidate a consensus value in IU. Additional study samples (such as clinical samples) will be included to provide an assessment of the suitability of the candidate to harmonise measurements of HHV-8 DNA in clinical samples.

	Methods will be selected to be representative of the range of commercial and laboratory-developed NAT-assays in use. Participants are anticipated to include ~10-15 laboratories representing both clinical laboratories and IVD manufacturers from different global regions.		
Issues raised by the proposal	There are no significant issues raised by the proposal.		
Proposer's project reference	SPL0093	**Date proposed:**	October 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (Recommendations for the preparation, characterization, establishment and use of WHO international biological reference standards. 2026)			
Approval status of medicinal product or in vitro diagnostic method that the IBRS is intended for; and the number of products (or diagnostic assays) that are in use	There are a number of CE- marked IVDs for the detection of HHV-8 DNA by NAT-based methods (there are currently no FDA-approved tests). Laboratory- developed tests (LDT) are also in use. Data from the INSTAND report of EQAS No. 406 Virus Genome Detection- HHV-8 (2025) reports the quantitative assay performance data from 5 different manufacturer IVDs and 16 LDTs, as well as qualitative assay performance data from 9 different manufacturer IVDs and 26 LDTs [5].		
Public health importance and global need for the IBRS from a regulatory and scientific perspective	HHV-8-associated disease in SOTR has historically been considered rare, with incidence broadly reflecting regional HHV-8 seroprevalence. An international survey conducted in 2021 found that only one-third of transplant centres routinely screened recipients for HHV-8, while two-thirds reported managing HHV-8-related complications [6]. Increasing reports of donor-derived HHV-8 transmission in Europe and the United States have heightened awareness of the need for donor screening and targeted virological monitoring of at-risk recipients to facilitate early diagnosis and intervention [2,3]. In the United States, transplant centres are required to report suspected donor-derived infections and malignancies to the Organ Procurement and Transplantation Network (OPTN). Analysis of these reports by the US Centers for Disease Control and Prevention (CDC) identified a five-fold increase in suspected donor-derived HHV-8 infections during 2021–2025 compared with the preceding five-year period [2]. Similarly, since surveillance began in 2012, HHV-8 has been the most frequently investigated donor-derived infection by the NHS Blood and Transplant Organ and Tissue Donation and Transplantation (OTDT) service in the UK [3]. Review of cases reported up to July 2021 identified seven clusters of primary HHV-8 infection in D+/R− SOTR, with a transmission rate of 48% and a case fatality rate of 64% [3]. These findings led to the introduction of universal HHV-8 screening of deceased organ donors in the UK in 2023. Donors with positive serological results are subsequently followed up by NAT testing of plasma and recipients are monitored by NAT to enable early detection of infection and timely clinical intervention. A WHO International Standard for HHV-8 DNA would support the development, validation, and harmonisation of NAT-based assays for donor screening and post-		

	transplant virological monitoring. This would improve identification of high-risk patients, facilitate early detection and treatment of infection, and enable comparison of assay performance across laboratories and platforms. Furthermore, standardisation of HHV-8 DNA measurement could support the development of harmonised clinical management strategies, including the establishment of clinically relevant viral load thresholds to guide therapeutic intervention. References: 1. Mesri *et al*. Kaposi's sarcoma and its associated herpesvirus. Nature Reviews (2010). 2. Kracalik *et a*l. Kaposi Sarcoma-Associated Herpesvirus Infection and Complications Among Solid Organ Transplant Recipients – United States, January 2021-September 2025. MMWR (2026). 3. SaBTO virology subcommittee recommendations on KSHV: full report (https://assets.publishing.service.gov.uk/media/67d0154374b001c38a0287a1/SaBTO-virology-subcommittee-recommendations-on-KSHV__1_.pdf) 4. Personal communication Ines Ushiro-Lumb, Clinical Microbiology Lead for Organ and Tissue Donation and Transplantation, Chair of UK SACTTI (2026). 5. INSTAND report of EQAS No. 406 Virus Genome Detection - HHV-8 (2025). 6. Mularoni A, et al. International survey of human herpes virus 8 screening and management in solid organ transplantation. Transplant Infectious Disease (2021).

Weak Anti-D Serological Reactivity

Proposal (title) including anticipated WHO IBRS category	International Reference Reagent for Weak Anti-D Serological Reactivity		
Proposer (name of Institution)	NIBSC (MHRA)	**Principal contact**	Dina Vara
Rationale	There is currently no WHO International Standard that defines serological Anti-D reactivity for use in indirect antiglobulin testing (IAT), gel/column agglutination, or other red-cell based serological methods. Existing WHO Anti-D standards (64/16 to 16/332) define immunoglobulin potency (IU) and are not commutable with serological assays. This gap affects global harmonisation of Anti-D detection, particularly for weak Anti-D, where sensitivity varies significantly between platforms and manufacturers. Laboratories lack a traceable, stable, internationally recognised material to verify the performance of Anti-D blood-grouping reagents and serological systems. A WHO International Standard for Serological Anti-D Reactivity would provide a globally harmonised benchmark for sensitivity, reactivity grading, and cross-platform comparability.		
Anticipated uses and users	Primary uses: Verification of weak Anti-D detection sensitivity, Calibration of internal serological QC materials, Harmonisation of reactivity grading across IAT, gel, CAT, and SPRCA platforms, Standardisation of Anti-D detection thresholds, Support for regulatory submissions and performance claims. Primary users: Transfusion laboratories, Blood services, Manufacturers of Anti-D blood-grouping reagents, External quality assessment (EQA) schemes, and Regulatory authorities		
Source/type of materials	The candidate preparation will consist of human plasma containing low-level IgG Anti-D pooled from multiple donors. All material will be prepared in accordance with WHO guidelines for biological reference materials. Candidate donations will be screened to confirm the absence of interfering alloantibodies and to ensure that the Anti-D reactivity falls within the desired weak range, such as 1+ or borderline detectable across methods. All donations will undergo mandatory infectious-disease screening (HIV, HBV, HCV, syphilis).		
Outline of proposed collaborative study	A multi-centre international collaborative study will be undertaken with participation from WHO collaborating centres, national blood services, serological platform manufacturers, and accredited reference laboratories. The candidate material will be assessed across all major serological methods, including tube IAT, multiple gel and column agglutination systems, solid-phase red-cell adherence assays, and enzyme-treated techniques, to ensure that its behaviour reflects the full range of technologies used in routine Anti-D detection.		

	Because serological Anti-D reactivity is a functional, method-dependent property rather than a quantitative biological activity, the preparation will be defined by a functional reactivity profile based on consensus responses across multiple assay platforms. The applicability of International Units (IU) will be assessed. While IU provides a measure of quantitative IgG potency, it assumes method-independent commutability. This assumption may not be fully met in agglutination-based serology, particularly in the weak Anti-D range, where non-linearity and method-dependent variability may limit robust assignment. Commutability will be assessed by comparing the candidate preparation with patient samples (if possible) and by evaluating its performance across different manufacturers' reagents. Stability will be examined through both real-time and accelerated studies. Statistical analysis will include modelling of reactivity curves and assessment of inter-laboratory variability to ensure that the assigned SRU value is robust, reproducible, and suitable for global use as a serological reference preparation.		
Issues raised by the proposal	The reference material will be defined by how it behaves in tests, rather than by a potency. There is currently no standard global approach for defining or using this type of material, there will need to be clear scientific justification and international agreement. It also needs to work across different testing methods (such as gel, tube, and solid phase), which all have different sensitivities. Because of this, the material may need to be defined slightly differently depending on the method, especially in the weak Anti-D range where results can vary between systems. Donor selection must ensure the absence of additional alloantibodies or confounding specificities that could compromise commutability or interpretation of reactivity patterns. It may be necessary to produce more than one version of the material (for example, "weak" and "very weak") so that laboratories can use it for different purposes, such as validation, checking sensitivity, and quality control.		
Proposer's project reference	SPL0089	**Date proposed**	04/06/2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (Recommendations for the preparation, characterization, establishment and use of WHO international biological reference standards. 2026)			
Approval status of medicinal product or in vitro diagnostic method that the IBRS is intended for; and the number of products (or diagnostic assays) that are in use	The proposed preparation supports widely used Anti-D serology assays (tube IAT, gel and solid phase) employed globally in clinical laboratories and blood services. These regulated IVD methods are used at high volume across multiple platforms and manufacturers. The reference reagent will therefore be applicable to many diagnostic assays and support improved standardisation of weak Anti-D detection. Based on anticipated use by IVD manufacturers, national control laboratories, blood services and specialist transfusion centres worldwide, demand is estimated at approximately 150–300 vials per		

	year, corresponding to a projected lifetime distribution of around 1,500–3,000 vials over a 10-year period. To ensure sufficient stock for global distribution, collaborative studies, stability monitoring and retained reserve samples, it is proposed that approximately 4,000 vials are produced, providing an adequate supply throughout the intended lifetime of the reagent.
Public health importance and global need for the IBRS from a regulatory and scientific perspective	Anti-D testing is widely used in transfusion medicine and antenatal care worldwide. However, variability between serological methods can lead to inconsistent detection of weak Anti-D. The proposed reference reagent addresses this gap by providing a functional benchmark for assay sensitivity, supporting improved consistency across laboratories and platforms. This is important for regulatory compliance, quality assurance, and patient safety at a global level.

Haemiglobincyanide (HiCN)

Proposal (title) including anticipated WHO IBRS category	Seventh International Standard for Haemiglobincyanide (HiCN)		
Proposer (name of Institution)	NIBSC (MHRA)	**Principal contact**	Dina Vara
Rationale	Haemoglobin measurement is one of the most common blood tests worldwide and is widely used in the diagnosis of anaemia, blood loss, and other clinical conditions. Current WHO International Standard for Haemiglobincyanide (NIBSC code 98/708) was established in 1998 to provide a primary reference for calibrating secondary standards and laboratory instruments. The material was produced by Diagnostic Reagents, and portions of the same batch were certified by the European Commission as Certified Reference Materials (CRM) 522/BCR-522 before being adopted by WHO. Because haemoglobin itself is inherently unstable, it's derivative, haemiglobincyanide, is used for measurement. The cyanmethaemoglobin method converts haemoglobin into haemiglobincyanide, which can be measured spectrophotometrically at ~540 nm. This procedure has been internationally recommended by the International Council for Standardisation in Haematology (ICSH) and WHO. Stocks of the WHO International Standard 98/708 are now running low. The reagent has served as the global reference for haemoglobin measurement, underpinning calibration of haemoglobinometers, spectrophotometers, automated blood cell counters and HiCN-based secondary standards. The WHO 98/708 standard was specifically established to support calibration of the cyanmethemoglobin reference method and associated reagents. Given its central role in maintaining world standardisation of haemoglobin results a replacement preparation is required to ensure continuity of haemoglobin measurement traceability.		
Anticipated uses and users	A replacement HiCN International Standard will serve as the primary reference material for haemoglobinometry and will support the calibration hierarchy for Haemoglobin measurement worldwide. The standard will primarily be used by manufacturers of in vitro diagnostic (IVD) systems and calibration material producers to assign values to secondary calibrators and control materials used in automated haematology analysers, haemoglobinometers, spectrophotometers, and other photometric measurement systems. Although many modern analysers employ alternative chemistries (e.g. sodium-lauryl-sulfate or azide-methemoglobin methods), these methods are expected to demonstrate comparability with reference procedures based on the cyanmethemoglobin method recommended by the International Council for Standardisation in Haematology. The International Standard may also be used by national and regional reference laboratories to maintain traceability of haemoglobin		

	measurements, support external quality assessment programmes, and verify secondary reference materials. In addition, it may be used by manufacturers and research laboratories involved in the development, validation, or evaluation of haemoglobin measurement methods.		
Source/type of materials	Fresh bovine blood collected into ACD (acid-citrate-dextrose) anticoagulant, and the haemoglobin converted to HiCN using cyanide-ferricyanide (Drabkin) reagent		
Outline of proposed collaborative study	The candidate replacement material will be evaluated in a collaborative study involving 8-10 expert laboratories with experience in haemoglobinometry and spectrophotometric analysis. Participating laboratories will measure the candidate preparation alongside the current WHO International Standard for haemiglobincyanide (NIBSC code 98/708). Measurements will be performed using spectrophotometric determination of haemiglobincyanide absorbance at 540 nm according to the recommended cyanmethemoglobin reference procedure. Laboratories will also assess material quality by determining the purity ratio (A540/A504) and turbidity (A750). The results will be used to assess the suitability of the candidate preparation and to assign a haemoglobin concentration relative to the current International Standard.		
Issues raised by the proposal	A potential issue in developing a replacement haemiglobincyanide (HiCN) International Standard is sourcing sufficient high-quality bovine blood. The material must be consistent, sourced from healthy animals meeting relevant veterinary and regulatory requirements, and screened as appropriate for relevant bovine pathogens and transmissible spongiform encephalopathy (TSE)/BSE risk. The material must also be suitable for producing a stable, homogeneous standard. As a chemically stabilised bovine derivative, it cannot fully demonstrate commutability with native human blood and may not behave identically in all routine assays, although it remains suitable for calibration and value assignment. Bovine blood is used because it can be processed to produce a highly purified and stable haemiglobincyanide preparation with excellent long-term storage characteristics and batch consistency. In contrast, the production of an equivalent standard from human blood would be more challenging because of limitations in sourcing large homogeneous batches, donor-to-donor variability, and additional ethical and regulatory considerations		
Proposer's project reference	SPL0088	**Date proposed**	04/06/2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (Recommendations for the preparation, characterization, establishment and use of WHO international biological reference standards. 2026)			
Approval status of medicinal product or in vitro diagnostic method	The HiCN International Standard supports widely used haemoglobin assays implemented across automated analysers and diagnostic platforms globally. These regulated IVD methods are used at high		

that the IBRS is intended for; and the number of products (or diagnostic assays) that are in use	volume in clinical laboratories and blood services worldwide. The standard underpins calibration and traceability for many assays across multiple manufacturers, making its replacement essential to maintain continuity and comparability of haemoglobin measurement. Annual demand is estimated at approximately 150–300 vials, corresponding to an anticipated lifetime distribution of around 2,000 vials over a 10-year period. To support global distribution, collaborative studies, stability testing and retained reserve stocks, approximately 4,000 vials is aimed to be produced.
Public health importance and global need for the IBRS from a regulatory and scientific perspective	Accurate haemoglobin measurement is essential for diagnosing anaemia, monitoring disease, ensuring donor safety, and supporting global health surveillance. The WHO haemiglobincyanide (HiCN) International Standard underpins harmonised haemoglobin measurement worldwide by providing traceability for calibration materials used across clinical laboratories and blood services. With current HiCN standard stocks nearly exhausted, there is a risk to global consistency in haemoglobin testing. A replacement standard is therefore critical to maintain calibration continuity, support regulatory compliance and quality assurance, and ensure ongoing comparability of results across laboratories worldwide.

Interleukin-1β

Proposal (title) including anticipated WHO IBRS category	Second WHO International Standard for interleukin-1β		
Proposer (name of Institution)	MHRA	**Principal contact**	Kata Dix
Rationale	The 1st WHO International Standard for interleukin-1β (IL-1β), NIBSC code 86/680, has been available since 1990. The usage of this reference material increased over time and currently up to 100 ampoules per year are distributed to customers globally. Filled originally in approximately 3000 ampoules, the existing stock is expected to deplete within the next four years. Initially termed human leukocytic pyrogen, IL-1β is a potent pro-inflammatory cytokine produced as a result of innate immune activation. Therapeutic products, targeted against IL-1β are available as monoclonal antibody (canakinumab), fusion protein (rilonacept), and competitive antagonist (anakinra). The use of anti-IL-1β therapies is indicated in a range of rare autoinflammatory and cardiovascular diseases. Further applications are being investigated in ongoing clinical trials, e.g. in the area of cancer immunotherapy. In addition to bioassays, IL-1β is also detected in a variety of immunoassays. Interleukin-1β is one of the recommended readouts for compendial Monocyte Activation Test (MAT) methods. The MAT is increasingly being adopted by pharmacopoeias as a replacement for traditional pyrogen testing methods.		
Anticipated uses and users	The main users of this standard are biological reagent and immunoassay manufacturers.		
Source/type of materials	The IS 86/680 and the available candidate materials are recombinant human IL-1β produced in *Escherichia coli*.		
Outline of proposed collaborative study	The proposed collaborative study will be a multi-centre international study, aiming for global coverage and focusing on using bioassays for potency calibration to the 1st IS 86/680. Immunoassays will also be included. At least one candidate preparation and the current IS will be included in the study.		
Issues raised by the proposal	None		
Proposer's project reference	SLP0034	**Date proposed**	October 2026
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (Recommendations for the preparation, characterization, establishment and use of WHO international biological reference standards. 2026)			

Approval status of medicinal product or in vitro diagnostic method that the IBRS is intended for; and the number of products (or diagnostic assays) that are in use	Anti-IL-1β therapeutics are available and biosimilars are being developed. A wide range of recombinant IL-1β reagents and immunoassays are marketed worldwide.
Public health importance and global need for the IBRS from a regulatory and scientific perspective	The continued availability of the IL-1β IS is essential for the global harmonization for the potency assignment of IL-1β preparations and antagonists.

Molecular weight calibration of low molecular weight heparin

Proposal (title) including anticipated WHO IBRS category	Third International Standard for Molecular weight calibration of low molecular weight heparin		
Proposer (name of Institution)	MHRA	**Principal contact**	John Hogwood
Rationale	The current material used as the calibrant to measure the molecular weight of low molecular weight heparin (LMWH) was prepared in the late 1990s. This single batch of material was used to prepare the current IS (NIBSC code: 05/112) and both the USP and the EP calibrants. The value assigned to the material – the broad standard table (BST) – is unified across all three references being established by the WHO ECBS in 2007 and adopted by the USP and EP. Although the USP and EP methods differ slightly, this does not affect the suitability of the material as a calibrant. While sufficient stocks of the IS are expected to last at least 20 years, EP/EDQM stocks will be exhausted within the next few years, followed by USP stocks. Given the harmonised nature of this reference material and the complexity of replacing it, a coordinated, joint approach is proposed to establish a replacement. Investigations indicate that a secondary calibrant would not be suitable, as it could disrupt LMWH manufacturers. Therefore, maintaining a single harmonised material is considered essential.		
Anticipated uses and users	All manufacturers of LMWH products are required to measure molecular weight as part of their manufacturing process, using this standard.		
Source/type of materials	Two potential options are being considered: a bespoke material and a mixed material. These have been identified through MHRA/NIBSC investigations into replacement strategies.		
Outline of proposed collaborative study	A two-phase study is proposed: • **Phase 1:** Evaluation of two candidate materials, from which a BST will be prepared. This phase will involve manufacturers only. • **Phase 2:** Verification study of the prepared BST, involving both manufacturers and additional laboratories.		
Issues raised by the proposal	The joint nature of this proposal introduces additional complexity, particularly in securing approvals from the relevant expert committees within USP and EP/EDQM.		
Proposer's project reference	SLP0041	**Date proposed**	Jun-2026

CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (Recommendations for the preparation, characterization, establishment and use of WHO international biological reference standards. 2026)	
Approval status of medicinal product or in vitro diagnostic method that the IBRS is intended for; and the number of products (or diagnostic assays) that are in use	Each LMWH has a characteristic molecular weight profile measured using this calibrant. These profiles are subject to strict regulatory, licensing, and pharmacopoeial requirements. Currently, eight LMWHs (INN: bemiparin, certoparin, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, tinzaparin) are in clinical use. Numerous generic and biosimilar products have also been developed following patent expiry.
Public health importance and global need for the IBRS from a regulatory and scientific perspective	This calibrant is essential for determining the molecular weight of LMWH products, which are widely used anticoagulants for conditions such as venous thromboembolic diseases. The International Standard, to which the USP Reference Standard (RS) and EDQM/EP Chemical Reference Substance (CRS) are harmonised, ensures continuity of measurement. Uninterrupted availability of the harmonised IS will help avoid disruption to LMWH manufacturers and support regulatory consistency worldwide.