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**Requests to initiate new WHO reference preparation projects for blood
products and in vitro diagnostic devices**

Document prepared by the WHO Secretariat, based on inputs from WHO
Collaborating Centres supporting biological standardization activities

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, each of which will be considered by the Expert Committee on Biological Standardization. The proposals have not yet been endorsed by the Expert Committee. Comments on the proposals MUST be received by 7 October 2011 and should be submitted electronically to the Responsible Officer: Dr Ana Padilla (padillaa@who.int).

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series.

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Introduction

The provision of global measurement standards is an important normative activity of WHO. Biological reference preparations that are accepted internationally enable the efficacy, quality, purity and safety of very many biological medicines, used in the prevention, treatment or diagnosis of disease or conditions, to be stated in a common language worldwide. International biological reference standards support the use of many biological and immunological assays for the quality control of a wide range of biologicals including therapeutics, blood-derived products, vaccines and immunological products of traditional types as well as those derived from modern biotechnological approaches. They also have important applications in the standardization of materials and approaches used in medical diagnostics such as diagnosing disease, monitoring therapy, blood safety, and public health applications (e.g. monitoring immune status, screening for disease or susceptibility) or otherwise characterizing biological material from individuals.

WHO biological reference standards are widely used in the development, evaluation, standardization and control of products by industry; by regulatory authorities; and also in biological research in academia and scientific organizations. They play a vital role in facilitating the transfer of laboratory science into worldwide clinical practice and the development of safe and effective biologicals.

The timely development of new reference standards and reference panels is critically important to harness scientific developments for new biologicals. At the same time, the active management of the existing inventory of reference preparations requires a carefully planned programme of work to replace established materials before the stock of containers, which comprises the standard, is exhausted.

Considerations for assignment of priorities to development of WHO International Biological Measurement Standards or Reference Reagents have been published (WHO TRS 932, Annex 2, Appendix 1, 2005). These considerations are used as guiding principles by the Secretariat and the WHO Collaborating Centres to develop a proposed programme of future work. To facilitate and to improve transparency in the priority setting process, a simple tool has been developed which describes the salient features of each new project proposal.

This document provides a means for the Committee and other stakeholders to review and comment on new proposals that are under consideration. The proposals in this document (WHO/BS/11.2179) cover requests to initiate new projects in the area of blood safety and in vitro diagnostic devices.

BLOOD PRODUCTS AND IN VITRO DIAGNOSTIC DEVICES**List of projects**

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*NAT: Nucleic Acid Amplification Techniques

Replacement of the 1st HIV -1 NAT Genotype Reference Panel

Proposal (title)	Replacement of 1st HIV -1 NAT Genotype Reference Panel		
Proposer (name of Institution)	NIBSC	Principal contact	Clare Morris
Rationale	HIV is a diverse virus with many different genotypes; due to the sequence differences and subsequent primer mismatches not all genotypes are detected effectively by both commercial and in-house assays. Sub-optimal detection of genotypes within the main M group of viruses has been reported as well as within diverse viruses in groups N and O. The first HIV-1 NAT Genotype Panel was produced in 2003. This panel is now depleted and a proposal to replace the panel is presented.		
Anticipated uses and users	A panel containing a selection of known genotypes allows manufactures to assess the limitations within an assay system. Kit manufacturers, blood banks and research laboratories will find this panel beneficial.		
Source/type of materials	NIBSC has sufficient stocks of viruses used in the original reference panel to formulate a replacement panel.		
Outline of proposed collaborative study	Up to 20 International laboratories with expertise in HIV testing would be asked to assess the panel. There are insufficient stocks of the 1 st panel for this to be included in the study. The 3rd HIV-1 IS will also be sent to participants for inclusion in all assays, this will assist in the possible assignment of a unit. As far as possible all commercial available assays will be included and laboratories from different geographic HIV related regions will be involved.		
Issues raised by the proposal	<p>The original panel was a liquid preparation stored at -80°C. However, in line with current HIV International Standards it is proposed that the panel members be formulated as lyophilised heat inactivated preparations. This option is supported by the WHO Collaborating centres (WHO CC) at the SoGAT meeting and this was also discussed at the 3rd WHO CC meeting in March 2011.</p> <p>The original panel contained a negative sample; it is proposed that this is not necessary in the replacement.</p>		
Action required	ECBS to endorse proposal		
Proposer's project reference	RET00015	Date proposed:	ECBS 2011
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	This is a relevant panel for regulatory approval of HIV-1 RNA tests internationally; it should also be used in the validation of IVD methods.		
Number of products or methods	There are currently different commercial assays involving different systems for HIV -1 NAT detection, both qualitative and quantitative, that can be assessed with this panel. The use of in house HIV NAT assays is also still quite high in some regions of the world due to the high cost of commercial applications. Such a panel is essential for the reliable development of future		

	assay systems for HIV-1 RNA detection in all regions.
Public health importance	It is known that not all assays are able to detect all genotypes with equal levels of accuracy. With the increase in global travel, HIV genotypes are not restricted to designated regions; therefore it is feasible that any genotype can be circulated in any given country. It is vital to know that detection of any genotype of HIV is reliable
Global importance	This panel has a global importance as HIV-1 NAT assays are in global use, whether they are commercial or in house,
Global need from regulatory & scientific considerations	No further considerations other than those already raised

Proposed 1st HIV-1 NAT CRF Reference Panel

Proposal (title)	Development of the 1 st HIV-1 NAT CRF Reference Panel		
Proposer (name of Institution)	NIBSC	Principal contact	Clare Morris
Rationale	<p>The diversity of HIV is well documented, in 2003 NIBSC produced an HIV-1 genotype panel to assist in the development of HIV assays across all subtypes. It is now widely appreciated that the recombinant nature of HIV has allowed the evolution of circulating recombinant forms of HIV whereby the virus may comprise of different genotypes across genomic regions. Often commercial and in house methods target one or two distinct regions, where variation exists across the genome there is a possibility of primer mismatch even on highly conserved regions. The development of a panel containing a selection of HIV recombinants will help to address this in assay design.</p>		
Anticipated uses and users	<p>A panel containing a selection CRF's and members of outlining groups allows manufacturers to assess the limitations within an assay system. This panel will be of benefit to kit manufacturers, blood banks and research laboratories.</p>		
Source/type of materials	<p>Stocks of 11 different viruses have been cultured and are in the process of characterization to assess for suitability for inclusion in this panel. Other viruses are available to the group through the Central Facility for AIDS Reagents at NIBSC should any of these viruses be unsuitable</p>		
Outline of proposed collaborative study	<p>Up to 20 International laboratories specializing in HIV testing would be asked to assess the panel. This must be a collaborative study including as many different geographical regions as possible (India, China, South America and African countries must be included where possible)</p>		
Issues raised by the proposal	none		
Action required	ECBS to endorse proposal		
Proposer's project reference	RET00012	Date proposed:	ECBS 2011
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	<p>This panel could be used in conjunction with commercial methods that are approved as IVD's.</p>		
Number of products or methods	<p>There are a range of different commercial assays that could be assessed with this panel. Such a panel is essential for the reliable development of both commercial and in house assay systems for HIV-1 NAT detection.</p>		
Public health importance	<p>It is known that not all assays are able to detect all genotypes with equal levels of accuracy. With the increase in global travel HIV genotypes are not restricted to designated regions; therefore it is feasible that any genotype can be circulated in any given country. It is vital to know that detection of</p>		

	any genotype of HIV is reliable
Global importance	This panel has a global importance as HIV-1 NAT assays, whether they are commercial or in house, are in global use.
Global need from regulatory & scientific considerations	No further considerations other than those already raised

Replacement of the 1st WHO International Standard for Hepatitis A Virus (HAV) for NAT

Proposal (title)	Proposed 2 nd WHO International Standard for Hepatitis A Virus (HAV) for Nucleic Acid Amplification Techniques (NAT)		
Proposer (name of Institution)	NIBSC	Principal contact	Jacqueline Fryer
Rationale	<p>The WHO International Standard for HAV RNA is used in the calibration of secondary reference materials and in the validation of HAV NAT assays used in the safety testing of solvent detergent-treated plasma. NAT is also widely used for the detection of HAV in environmental and clinical samples.</p> <p>As of June 2011, the existing stock of the current 1st HAV IS (00/560) is ~500 vials. Approximately 150 vials of this standard are issued each year, therefore stocks are likely to be exhausted ~3-4 years. The replacement will require up to 2 years for completion.</p>		
Anticipated uses and users	Used to calibrate secondary reference materials and in the validation of HAV NAT assays. Anticipated users are; blood product manufacturers, clinical laboratories, control authorities, and IVD manufacturers.		
Source/type of materials	<p>The current HAV International Standard (00/560) was prepared from a wild-type isolate derived from human plasma, and was filled and freeze-dried in 2001. At the time of preparation a potential replacement candidate was also prepared from the same bulk (00/562). However, continued stability assessment of accelerated thermal degradation samples from this batch suggested that there was some loss of potency ($\sim 1\log_{10}$) upon storage at +4°C (WHO/BS/07.2056). Further stability studies are ongoing, however, the replacement will likely comprise a new stock of the same genotype of HAV. This will be diluted in pooled human plasma to a concentration of 10⁵ IU/mL. The formulation was discussed at the SoGAT Blood Virology workshop in April 2011.</p>		
Outline of proposed collaborative study	<p>The collaborative study will involve 20-30 laboratories worldwide, performing a range of HAV NAT-based methods, and representing IVD manufacturers, manufacturers of plasma products, control authorities and clinical laboratories.</p> <p>Study samples; candidate replacement standard and the 1st HAV International Standard (00/560).</p>		
Issues raised by the proposal	None		
Action required	ECBS to endorse proposal		
Proposer's project reference		Date proposed:	ECBS 2011
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	NAT is the recommended method for the detection of HAV RNA in human plasma (pooled and treated for virus inactivation) [European Pharmacopoeia monograph 01/2011:1646]. Assays are required to detect 100 IU/mL HAV RNA.		

Number of products or methods	A range of NAT-based methods are available for the detection and quantification of HAV RNA, including both commercial and laboratory-developed assays.
Public health importance	The need to standardize NAT-based assays for HAV is ongoing. NAT is widely used for the detection of HAV in environmental and clinical samples.
Global importance	HAV is responsible for approximately half of the cases of hepatitis diagnosed worldwide. It is also recognized as one of the most important human food-borne pathogens affecting people in the Western world.
Global need from regulatory & scientific considerations	In the EU, it is a requirement that solvent detergent-treated plasma is screened for HAV RNA [European Pharmacopoeia monograph <i>Human plasma pooled and treated for virus inactivation (1646)</i>].

Proposed 1st International HBe Antigen (HBeAg) Standard

Proposal:	Proposed 1 st International HBe Antigen (HBeAg) Standard		
Proposer:	Paul-Ehrlich-Institute (PEI)	Principal Contact	Annette Reissinger, Sigrid Nick
Rationale:	<p>Preparation of a new HBe Antigen standard</p> <ul style="list-style-type: none"> • Scientific background: Hepatitis B virus (HBV) infection is a major health problem worldwide with estimated 350 million chronic carriers. It is presumed that about one third of the human population have once encountered the virus. The HBeAg is a diagnostic marker for HBV infectivity and circulates in patient blood when the virus is actively replicating. • Market background: PEI ships HBeAg Material ("PEI Reference-Antigen 82") worldwide with high demand (approx. 50 ampoules/year), largely to manufacturers. • Historic background: PEI Material has been used since 1982 and many manufacturers have referred the HBeAg concentration in PEI units. • Regulatory background: European legislation (Common Technical Specifications 2009/886/EC) require an HBeAg standard for determination of analytical sensitivity. Currently, the Paul-Ehrlich-Institut HBeAg standard is used. 		
Anticipated Uses and Users:	Determination of the analytical sensitivity of HBeAg assays. It may also serve for calibration of secondary standards by manufacturers of diagnostic kits, for quality control by competent authorities and by users.		
Source/Type of Materials:	Antigen-positive human serum or plasma.		
Outline of proposed collaborative study	Value assignment may be performed in an international collaborative study involving reference laboratories, test kit manufacturers and competent authorities (10 -15 laboratories).		
Issues raised by the proposal:	None		
Actions required:	Identify and source suitable materials, characterize the materials for antigen content and infection markers (HIV, HCV), perform stability evaluation and investigate stability in the context of lyophilization, performance of feasibility study. Once the study demonstrates suitability of the preparation, results will be presented to WHO. If accepted by WHO, the collaborative study will be initiated.		
Ref:		Date proposed:	ECBS 2011

Addendum to Proposal for development of 1st International HBe Antigen (HBeAg) Standard

Proposal:	Proposed 1 st International HBe Antigen (HBeAg) Standard	
Actions:	Responsibility	Timeline
Current PEI Standard	The current PEI Human HBeAg "PEI Reference-Antigen 82" is liquid serum and is stored at -80 °C	n.a.
Purpose	PEI-U to be transferred to IU	n.a.
Amount	2300 ampules in 0,5 ml aliquots: equals 1150 ml	n.a.
Lyophilisation	PEI	End of 2011
Feasibility study	A feasibility study will be performed by PEI to examine the potential influence of the freeze-drying on the activity	Jan 2012
Collaborative study (CS)	10-15 external laboratories; no further sample will be included in the CS	Feb 2012 – Apr 2012
Commutability	The "PEI Reference-Antigen 82" has been established in 1982; the current concentration is 100 PEI-U/ml	n.a.
Storage	PEI, at +2-8 °C	n.a.
Shipping	The shipping of the standard will be carried out by PEI	n.a.
Custodianship	PEI	n.a.

Proposed 1st International anti-HBe IgG Standard

Proposal:	Proposed 1 st International anti-HBe IgG Standard		
Proposer:	PEI	Principal Contact	Olivia Knauer/ Heiner Scheiblauer
Rationale:	<p>Hepatitis B virus (HBV) infection is spread worldwide. About 2 billion people worldwide have been infected with the virus and about 350 million live with chronic infection.</p> <p>The diagnosis of HBV requires a combination of various tests including detection of antibodies to HBe antigen (anti-HBe). The anti-HBe test is particularly meaningful in association with the HBeAg test for monitoring the course of HBV infection. Anti-HBe without HBeAg can indicate the presence of the precore stop codon mutants.</p> <p>The Paul-Ehrlich-Institut (PEI) anti-HBe IgG-material (high titer human serum) has been used since 1982 for calibration of the anti-HBe kits and many manufacturers have referred the sensitivity to PEI units. There is a demand for anti-HBe which is currently 10 ampoules per year.</p>		
Anticipated Uses and Users:	Determination of the analytical sensitivity of anti-HBe assays. It may also serve for calibration of secondary standards by manufacturers for their test kits, for quality control by competent authorities and by users.		
Source/Type of Materials:	Human serum or plasma positive for antibodies to HBe antigen (anti-HBe)		
Outline of proposed collaborative study	The candidate reference material will be the existing PEI anti-HBe material. Value assignment in IU will be performed in an international collaborative study involving reference laboratories, test kit manufacturers and competent authorities.		
Issues raised by the proposal:	None		
Actions required:	If the proposal is accepted by ECBS, a collaborative study will be initiated.		
Ref:		Date proposed:	ECBS 2011

Addendum to Proposal for development of 1st International anti-HBe IgG Standard

Actions:	Responsibility	Timeline
Current PEI standard	The current PEI Human anti-HBe standard is liquid serum and stored at -80 °C.	n.a.
Purpose	Current PEI-U to transfer in IU	June 2012
Amount	1600 ampoules equivalent to 800 ml in 0.5 ml filling volume.	n.a.
Lyophilisation	By PEI	End of 2011
Feasibility study	A feasibility study will be performed by PEI to examine the potential influence of the freeze-drying on the activity.	Jan 2012
Collaborative study	10-15 external laboratories No further sample will be included in the studies.	Feb 2012 – Apr 2012
Commutability	The standard has been established in 1982, the current concentration is 100 PEI-U/ml. Most of the manufacturers already use this material (anti-HBe IgG Referenzserum 82) for determining the analytical sensitivity of their assays and for calibration.	n.a.
Storage	PEI at 2-8 °C	June 2012
Shipping	The shipping of the standard will be carried out by PEI.	June 2012
Custodianship	PEI	June 2012

Proposed 1st Hepatitis E Virus Genotype Panel for NAT

Proposal (title)	Hepatitis E Virus Genotype Panel for NAT-Based Assays		
Proposer (name of Institution)	PEI	Principal contact	Sally Baylis
Rationale	<p>The candidate International Standard (IS) for hepatitis E virus (HEV) RNA (PEI code number 6329/10) is to be considered for endorsement at the ECBS meeting in October 2011. The candidate IS has been prepared from a genotype 3a HEV strain, obtained from a Japanese blood donor, which was well-detected by participating laboratories in both an initial pilot study and the follow-up collaborative study to investigate the potency/suitability of the candidate material.</p> <p>Whilst HEV is represented by a single serotype, the virus can be classified into at least four main genotypes. Genotypes 1 and 2 can be found in humans, whilst genotypes 3 and 4 are found in both humans as well as a range of animal species, particularly pigs and wild boar where the sequences between the animal and human strains, circulating in the same geographic region, are closely related with evidence for zoonotic infection.</p> <p>The geographical distribution of HEV genotypes is complex. Genotype 1 consists of strains circulating in Africa and Asia (Egypt, Algeria, Morocco, Sudan, and Chad; India, Pakistan, Nepal, Bangladesh and China). Genotype 2 is found in Mexico and in some African countries (Nigeria, Namibia, Chad, and Sudan). Genotype 3 is widely distributed, mainly being reported in the USA, Europe and Japan. Genotype 4 is restricted to India and East Asia. However, genotype 1 viruses, and more recently genotype 4 viruses, are found in patients in Europe, North America and elsewhere after travelling to endemic areas and represent imported cases. Epidemics and sporadic cases of hepatitis E occur in areas of endemicity (genotypes 1, 2 and 4); more isolated clinical cases occur among a sizeable group of mostly asymptomatic seropositive residents in developed countries (genotype 3). There is increasing evidence of chronic infection with genotype 3 HEV in transplant patients with monitoring of viral loads in response to antiviral therapy.</p> <p>From sequence analysis of different HEV strains, at the nucleotide level, there is in the order of 74% nucleotide identity between genotypes. In the case of genotype 3 for example, there are at least 10 sub-genotypes which vary by up to 15% nucleotide identity. In order to ensure appropriate coverage of NAT assays for HEV, the availability of a genotype panel would be a valuable tool. In the study to evaluate the candidate IS, a single assay was widely used which, through differences in implementation assay sensitivities were quite varied even for the two virus strains included in the study.</p>		
Anticipated uses and users	Clinical laboratories, particularly hepatitis reference laboratories. Blood banks, plasma fractionation organizations and associated control laboratories. In some places, food handlers are tested for HEV infection. Research laboratories and organizations developing HEV vaccines. IVD manufacturers.		
Source/type of materials	Additional HEV strains are available from the original pilot study. Further HEV samples will be obtained from blood/plasma collection centres and from clinical laboratories. Some of the laboratories who participated in the initial pilot study, and the subsequent collaborative study to evaluate the candidate IS, are reviewing their sample archives and others are		

	prospectively collecting samples. The samples will represent different genotypes, and sub-genotypes and samples which challenge some of the common assays used.		
Outline of proposed collaborative study	Samples will be analyzed alongside 6329/10. Participants in the recent collaborative studies (~20-23 laboratories) have confirmed that they are willing to participate in a further collaborative study if the proposal to prepare a genotype panel is endorsed.		
Issues raised by the proposal	As an adjunct to the study, commutability of 6329/10 will be investigated subject to collection of suitable samples and identification of appropriate assays.		
Action required	ECBS to endorse proposal		
Proposer's project reference		Date proposed:	ECBS 2011
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	The vast majority of HEV NAT assays have been/are developed in-house. A single commercial assay was included in the original pilot study and targets genotypes 1 and 4. The company is ISO 13485 certified, however the kit is not CE-marked. Other organizations have assays in development.		
Number of products or methods	As above.		
Public health importance	To ensure that assays are able to detect different genotypes and sub-genotypes of HEV which may be both locally acquired or imported after travel to different endemic areas.		
Global importance	HEV infection occurs worldwide with different epidemiology. It is recognized as an emerging infection, with certain genotypes being zoonotically acquired. A genotype panel must reflect this diversity.		
Global need from regulatory & scientific considerations	As above.		

Replacement of the 3rd International Standard for Plasmin

Proposal (title)	Replacement of the 3rd International Standard for Plasmin		
Proposer (name of Institution)	NIBSC	Principal contact	Craig Thelwell
Rationale	The WHO 3rd IS for plasmin (97/536) is used to standardize fibrinolysis assays. With depleted stocks and a renewed interest in plasmin as a thrombolytic drug a replacement IS is needed.		
Anticipated uses and users	To standardize potency assignment of therapeutic plasmin by manufacturers, and to standardize plasmin potency measurements in fibrinolysis assays.		
Source/type of materials	Purified enzyme from human plasma. One pharmaceutical manufacturer identified.		
Outline of proposed collaborative study	The study will use the existing standard to calibrate the new standard in IU. In addition the molar concentration will be determined by active-site titration.		
Issues raised by the proposal	There are few manufacturers of plasmin, or laboratories that routinely measure its activity, so recruitment to the study may be difficult and the size of the study will be small.		
Action required	ECBS to endorse proposal		
Proposer's project reference	BIO 00046	Date proposed:	ECBS 2011
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	Plasmin, as a direct acting thrombolytic, is in developmental Phase II for the treatment of acute peripheral arterial occlusion, and Phase I for acute ischemic stroke. Microplasmin (a truncated form that retains enzymatic properties) is in Phase III for Vitreomacular adhesion treatment, and Phase II for Diabetic retinopathy and age-related macular degeneration.		
Number of products or methods	Chromogenic, fibrin-clot based and active-site titration methods are in routine use.		
Public health importance	Development of plasmin as a new thrombolytic drug is of significant public health importance		
Global importance	The IS is used worldwide, mostly to standardize fibrinolysis assays at present.		
Global need from regulatory & scientific considerations	With the emergence of plasmin as a thrombolytic drug it is important that the new plasmin IS is representative of therapeutic grade products, and is appropriate to standardise potency assignment between current and any future products developed worldwide.		

Replacement of the 2nd International Reference Reagent for Serum IgE

Proposal (title)	Replacement of the 2 nd International Reference Reagent for serum IgE		
Proposer (name of Institution)	NIBSC	Principal contact	Susan Thorpe
Rationale	Serum IgE measurements are essential for the diagnosis and management of allergic disorders.		
Anticipated uses and users	Manufacturers of diagnostic tests and clinical laboratories.		
Source/type of materials	Pooled sera from patients with allergic disorders.		
Outline of proposed collaborative study	Replacement preparation will be calibrated against the 2 nd IRR by users of the latter.		
Issues raised by the proposal	Possible difficulties in sourcing suitable plasma or serum: identifying suitable donors, and obtaining appropriate consent and ethical approval.		
Action required	ECBS to endorse proposal.		
Proposer's project reference	00022	Date proposed:	ECBS 2011
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	In vitro diagnostic test(s) for allergen-specific IgE in serum.		
Number of products or methods	Several commercial and in-house diagnostic tests.		
Public health importance	Allergic disorders are common and incidence is increasing.		
Global importance	The IRR is used worldwide.		
Global need from regulatory & scientific considerations	There is frequent demand for the current Reference Reagent, stocks of which are nearing exhaustion. Replacement is needed for continuation of standardisation and comparability of test results across laboratories.		