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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 17 to 20 October 2017

Requests to initiate new WHO reference material projects for vaccines and related substances

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Comments MUST be received by **18 September 2017** and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Technologies, Standards and Norms (TSN). Comments may also be submitted electronically to the Responsible Officer: **Dr I. Knezevic** at email: knezevici@who.int. The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series.

Appendix 1 Vaccines and related substances

Proposed new projects

Proposal (title)	**1st International Standard panel for Lipopolysaccharide of *Vibrio cholerae* O1 Inaba, O1 Ogawa and O139**		
Proposer (name of Institution)	NIBSC	**Principal contact**	Sjoerd Rijpkema, Bacteriology
Rationale	*Vibrio cholera* O1 and O139 are a leading cause of bacterial diarrhea bacteremia in Africa, South east Asia and the Caribbean. Cholera outbreaks occur frequently in refugee camps and following natural disasters. Young children and infants are particularly vulnerable. Oral Cholera Vaccine Inactivated is the most cost- effective measure to contain and prevent this disease in these settings. WHO has undertaken to build a stockpile which is supported by vaccine manufacturers, 3 to date. The availability of WHO standards for LPS of O1 Inaba, O1 Ogawa and O139 *V cholerae* would enhance and support further development of the production and technology transfer of cholera vaccines.		
Anticipated uses and users	Anticipated usage for LPS O1 Inaba, O1 Ogawa and O139 will be used by National Control Laboratories and vaccine manufacturers to calibrate immunoassays used to determine the potency of Oral Cholera Vaccine batches. Estimated use is approx. 10 vials per year.		
Source/type of materials	Purified LPS O1 Inaba, O1 Ogawa and O139 will be obtained from the International Vaccine Institute. The material will be filled and freeze died at NIBSC. Approximately 1000 ampoules of each serotype would be produced.		
Outline of proposed collaborative study	An NIBSC collaborative study will be required: • To assess the suitability of the candidate standards as an IS for LPS of O1 Inaba, O1 Ogawa and O139 in the Inhibition ELISA to determine the potency of Oral Cholera Vaccines. • To compare the reactivity of the candidate standards and in-house standards in in-house Inhibition ELISAs. The participants will be vaccine developers/manufactures and National Control Laboratories and is likely to be quite small. The CS will establish whether the material is 'fit for purpose'. At NIBSC, biochemical and biophysical characterization of the LPS will be carried out and the specification will be aligned to criteria of the current literature.		
Issues raised by the proposal			
Action required	Evaluation by Committee for integration into NIBSC work plan.		
Proposer's project		**Date proposed:**	

reference			
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	Oral cholera vaccines play an important role in the control and prevention of Cholera outbreaks, and three have been PQ-ed by WHO and are part of a WHO maintained stockpile. Thus proper reference reagents are important for the QC these vaccines and to compare products.		
Number of products or methods	3-4 new manufactures from LMICs will enter the field.		
Public health importance	Cholera outbreaks are the cause of massive disruption and considerable mortality in refugee camps or local areas of poorly resourced countries. For example in the 2011 Haiti outbreak an estimated 779,000 cases of cholera and 11,100 deaths occurred. Vaccination of 10% of the population would have averted 63,000 cases and 900 deaths.		
Global importance	The Haiti epidemic was caused by the transfer of highly virulent *V cholera* O1 strains endemic to Nepal. This is an example of the rapid global expansion of this disease.		
Global need from regulatory & scientific considerations	To be effective Cholera vaccines will need by properly regulated at National levels to ensure comparable efficacy. Standardisation is a pre-requisite to achieve this.		
ECBS outcome			

Proposal:	**1st International Standard Serum Panel of anti-*Vibrio cholerae* O1 and O139 LPS serum (Rabbit)**		
Proposer:	NIBSC	**Principal Contact**	Sjoerd Rijpkema
Rationale:	*Vibrio cholera* O1 and O139 strains are a leading cause of bacterial diarrhea bacteremia in Africa, South east Asia and the Caribbean. Cholera outbreaks occur frequently in refugee camps and following natural disasters. Young children and infants are particularly vulnerable. Oral Cholera Vaccine Inactivated is the most cost- effective measure to contain and prevent this disease in these settings. WHO has undertaken to build a stockpile which is supported by vaccine manufacturers, 3 to date. The availability of anti-O1 and anti-O139 serum panel as WHO standards will enhance and support the development of the production and technology transfer of new cholera vaccines.		
Anticipated Uses and Users:	Rabbit antisera for O1 Inaba, O1 Ogawa and O139 will be used by National Control Laboratories and vaccine manufacturers to calibrate immunoassays used to determine the potency of Oral Cholera Vaccine batches. Estimated use is approx. 10 vials per year.		
Source/Type of Materials:	The proposal is part of a joint effort with IVI and BMGF and aims to produce three sets of sera in rabbits: anti-O1 Inaba serum, anti-O1 Ogawa serum and anti-O139 serum at NIBSC. The materials will be filled and freeze-dried. Approx. 500 ampoules with 1 mL each will be made available.		
Outline of proposed collaborative study	An NIBSC collaborative study will be required: • To assess the suitability of the candidate standards as an IS for anti-O1 Inaba, anti-O1 Ogawa and anti-O139 in the Inhibition ELISA to determine the potency of Oral Cholera Vaccines. • To compare the reactivity of the candidate standards and in-house standards in in-house Inhibition ELISAs.		
Endorsement prior to ECBS:	Supported by IVI and BMGF.		
Issues raised by the proposal:	• The serum standards will be used to compare potency and stability of vaccines to a standard Cholera Vaccine. • The serum standards will facilitate technology transfer to vaccine manufactures and National Control Laboratories in resource-poor countries.		
Action required:	Evaluation by the Committee for integration into NIBSC work plan.		
NIBSC Ref:			

Approval status of medicine or in vitro diagnostic method	Oral cholera vaccines play an important role in the control and prevention of Cholera outbreaks, and three have been PQ-ed by WHO and are part of a WHO maintained stockpile. Thus proper reference reagents are important for the QC these vaccines and to compare products.
Number of products or methods	3-4 new manufactures in LMIC will enter the field.
Public health importance	Cholera outbreaks are the cause of massive disruption and considerable mortality in refugee camps or local areas of poorly resourced countries. For example in the 2011 Haiti outbreak an estimated 779,000 cases of cholera and 11,100 deaths occurred. Vaccination of 10% of the population would have averted 63,000 cases and 900 deaths.
Global importance	The Haiti epidemic was caused by the transfer of highly virulent *V cholerae* O1 strains endemic to Nepal. This is an example of the rapid global expansion of this disease.
Global need from regulatory & scientific considerations	To be effective Cholera vaccines will need by properly regulated at National levels to ensure comparable efficacy. Standardisation is a pre-requisite to achieve this.
ECBS outcome	

Proposal (title)	**First International Standard for V cholera vaccine Oral Inactivated**		
Proposer (name of Institution)	NIBSC	**Principal contact**	Sjoerd Rijpkema, Bacteriology
Rationale	*Vibrio cholera* O1 and O139 strains are a leading cause of bacterial diarrhea in Africa, South-East Asia and the Caribbean. Cholera outbreaks occur frequently in refugee camps and following natural disasters. Young children and infants are particularly vulnerable. Oral Cholera Vaccine Inactivated is the most cost- effective measure to contain and prevent this disease in these settings. WHO has undertaken to build a stockpile which is supported by vaccine manufacturers, 3 to date. The availability of a mixture of killed *V cholera* O1 Inaba, O1 Ogawa and O139 whole cells in a composition similar to the vaccine will enhance and support further development of assay required to ascertain the quality and for technology transfer of cholera vaccines.		
Anticipated uses and users	National Control Laboratories and vaccine manufacturers will use these standards to calibrate immunoassays used for release, stability and potency of final lots of the Oral Cholera Vaccine and if required to characterise its drug substance bulks. Estimated use is approx. 10 vials per year.		
Source/type of materials	The proposal is part of a joint effort with IVI and BMGF and aims to produce a standard vaccine based on killed cells of *V cholerae* O1 Inaba/Ogawa and O139 cells. Approx. 1000 ampoules with 1 mL of freeze dried of frozen cell will be made available.		
Outline of proposed collaborative study	The material will be used in a CS to assess the suitability of candidate IS for a standard vaccine in in-house inhibition ELISAs to determine the potency of Oral Cholera Vaccines.		

Issues raised by the pr oposal	Working with not-for profit organizations will limit CoI.		
Action required	Evaluation by the Committee for integration into NIBSC work plan.		
Proposer's project reference		**Date proposed:**	
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	Oral cholera vaccines play an important role in the control and prevention of Cholera outbreaks, and three have been PQ-ed by WHO and are part of a WHO maintained stockpile. Thus proper reference reagents are important for the QC these vaccines and to compare products.		
Number of products or methods	3-4 new manufactures in LMIC will enter the field.		
Public health importance	Cholera outbreaks are the cause of massive disruption and considerable mortality in refugee camps or local areas of poorly resourced countries. For example in the 2011 Haiti outbreak an estimated 779,000 cases of cholera and 11,100 deaths occurred. Vaccination of 10% of the population would have averted 63,000 cases and 900 deaths.		
Global importance	The Haiti epidemic was caused by the transfer of highly virulent *V cholerae* O1 strains endemic to Nepal. And is an example of the rapid global expansion of this disease.		
Global need from regulatory & scientific considerations	To be effective Cholera vaccines will need by properly regulated at National levels to ensure comparable efficacy. Standardisation is a pre-requisite to achieve this.		
ECBS outcome			

Proposal (title)	**1st International Standard for antibody to the influenza virus haemagglutinin stem domain**		
Proposer (name of Institution)	NIBSC	**Principal contact**	Othmar Engelhardt
Rationale	Many antibodies binding the stem domain of the haemagglutinin (HA) of influenza A viruses have been found to be cross-reactive between drifted viruses of the same subtype as well as between viruses of different subtypes, at least in some cases. Consequently, attempts are underway to develop vaccines that elicit HA stem-binding antibodies; such vaccines have the potential to be broadly reactive and protective. Various assays are used to measure HA stem-binding antibodies, including virus neutralisation assays and binding assays. The exact relationship and correlation between results obtained using different methods are not known. As some vaccine candidates progress through pre-clinical and clinical testing, harmonization of serologic read-outs is desirable. Vaccine developers will attempt to define correlates of protection (CoPs) for these new types of vaccine. It would be useful if such CoPs are measured and expressed in a way that is comparable between laboratories and studies. An International Standard can help to achieve better comparability and harmonization of assay results.		
Anticipated uses and users	It is expected that laboratories developing new generation influenza vaccines targeting the stem region of the HA, laboratories working on HA stem binding antibodies and serologic laboratories will use this standard to standardize their assays. The International Standard will also be useful in the determination of new correlates of protection for new influenza vaccines.		
Source/type of materials	The best format for an International Standard is not yet clear. It is proposed that NIBSC acquires several monoclonal antibodies that bind overlapping and non-overlapping epitopes on the stem domain of the HA. Antibodies may be combined in an oligoclonal mix. Polyclonal antisera raised against the HA stem domain may also be of use. Samples from human clinical trials of new vaccine candidates will be sought from vaccine developers.		
Outline of proposed collaborative study	It is likely that this standard will be developed in two phases. In a first phase, candidate materials as outlined above will be sent to a small number of laboratories and tested in their in-house tests for HA stem-binding antibodies. They will also be compared to animal or human serum samples from studies with new vaccine candidates, and the ability of the candidate standard materials to harmonise results will be assessed. Based on this first study, a second, larger study will include the best performing types of standard as identified in the first study, as well as samples from human clinical trials.		
Issues raised by the	It is not yet known whether a single monoclonal antibody, an oligoclonal mix		

proposal	of monoclonal antibodies or a polyclonal antiserum (of human or animal origin) will perform best as a standard. Therefore, this project will be composed of two phases and will therefore take more time than many common standardization projects. Obtaining monoclonal antibodies from commercial entities may involve lengthy MTA negotiations.		
Action required	ECBS to endorse proposal		
Proposer's project reference		**Date proposed:**	
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	A number of laboratories are developing vaccines targeting the stem domain of influenza virus HA. First clinical trials are expected soon. In addition, laboratories are developing therapeutic monoclonal antibodies against the HA stem domain. The latter may also benefit from an International Standard.		
Number of products or methods	Different methods are used, both functional (eg, virus neutralization assays, ADCC) and binding assays (eg, ELISA) by a number of laboratories.		
Public health importance	The need for better, more broadly protective and longer lasting influenza vaccines has been recognized for many years, including by WHO (eg, WHO is developing Preferred Product Characteristics for new influenza vaccines). Such vaccines have the potential to improve the public health response to seasonal and pandemic influenza. Vaccines targeting the conserved HA stem domain are among the promising candidates for new, better influenza vaccines, but there are other vaccine concepts for which this proposed standard would not work.		
Global importance	New influenza vaccines will have a public health impact world-wide, in high and low income countries.		
Global need from regulatory & scientific considerations	New influenza vaccines will most likely be authorised based on vaccine efficacy data. However, the determination of correlates of protection is highly desirable from the perspective of both regulators and vaccine developers. An International Standard will make studies more comparable and aid the definition of new CoPs.		
ECBS outcome	[BLANK]		

Proposal (title)	**Influenza virus pathogenicity standards for safety testing**		
Proposer (name of Institution)	NIBSC	**Principal contact**	Othmar Engelhardt
Rationale	Safety testing of influenza candidate vaccine viruses (CVVs) involves a test in ferrets, whereby the CVV is compared to its parental wt virus; the CVV must be attenuated relative to the corresponding wt virus. There are currently no accepted criteria for attenuation. TRS941, Annex 5, which specifies safety testing for CVVs, is currently under review. It has been proposed that standards of pathogenicity could be used instead of reliance on wt viruses specific for each CVV. The reference/standard viruses will be used to benchmark each laboratory's ferret test: cut-off points or ranges (for pathogenicity and/or attenuation) can be defined based on previously generated data with various CVVs and wt viruses and compared, in a collaborative study, with the proposed reference viruses. In the future, the reference viruses will be used from time to time in each laboratory to ensure the robustness of the ferret safety test. Use of standard viruses in this way in combination with defined cut-off values/ranges will reduce the number of animals used and, in addition, provide a means to assess CVVs the parental wt viruses of which are non-pathogenic in ferrets (such CVVs cannot currently be demonstrated to be attenuated as per the existing WHO guidance).		
Anticipated uses and users	Laboratories generating influenza CVVs for zoonotic/pandemic/pre-pandemic influenza viruses will use the reference viruses occasionally to check whether their ferret pathogenicity test performs within pre-defined limits. CVVs can then be compared to the reference viruses. The reference viruses can also be used in case of new laboratories entering the field or when major changes to a laboratory's ferret safety test have occurred (eg, move of laboratories, new supplier of ferrets). The number of users is approximately 5 – 7 laboratories (current status). Should a CVV testing laboratory contract out a test, the reference viruses could be used to establish the test in the new facility. This would provide assurance to all parties in support of the validity of the data generated.		
Source/type of materials	Wild-type (wt) viruses and CVVs. NIBSC has many and can obtain more through the WHO GISRS. Growing up of stocks can be performed in-house. No donation of material that will be used directly as standard is required.		
Outline of proposed collaborative study	Laboratories experienced in the ferret safety test will be asked to conduct the test on the candidate standard viruses and to feedback data to NIBSC. Data will include virus titres in organs, virus shedding, body temperature, body weight and clinical observations. Together with data from studies done by these laboratories in the past, ranges and/or cut-offs for important read-outs (eg, viral load in the lung, in nasal turbinates, weight loss, etc) will be set that define (1) a level of pathogenicity that is unacceptable for a CVV, ie a threshold below which any CVV must be found to be and (2) a level of pathogenicity that is considered 'attenuated', ie a range that qualifies a CVV as an attenuated CVV if the values for the CVV fall within (or below) the		

	range.		
Issues raised by the proposal	None		
Action required	ECBS to endorse proposal		
Proposer's project reference		**Date proposed:**	
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	This relates to the development of CVVs for influenza vaccines for pandemic preparedness purposes. Such CVVs are generated on a continual basis and need to be assessed for attenuation. It is proposed that use of the standard viruses will be included in the revised version of TRS941, Annex 5.		
Number of products or methods	Many similar influenza vaccines world-wide that require CVVs. Methods differ to some degree between laboratories, but all follow general WHO guidance.		
Public health importance	CVVs are of crucial importance for the production of influenza vaccines. In the case of a pandemic, these need to be generated and tested very rapidly. Having the proposed standard viruses available before a pandemic enables laboratories to harmonise their safety testing. In the event of a pandemic when access to a newly emerging wt virus may be difficult, tests can be conducted faster with the result that CVVs may be released sooner without compromising safety. Ultimately with fewer animals being required to conduct a test a greater range of CVVs could be tested in a pandemic situation if needed.		
Global importance	There are only a few laboratories that generate and/or test influenza CVVs; however, these laboratories supply all manufacturers of conventional influenza vaccines with CVVs.		
Global need from regulatory & scientific considerations	Animal tests can be variable, and the ferret safety test is no exception. Having standards that allow the bench-marking of the test will lead to better understanding of and higher confidence in results of ferret safety tests. Moreover, this proposal is in line with the move towards reduction of use of animals in research and development of biological medicines: instead of comparing every new CVV with its respective wt parental virus, occasional testing of the standard viruses would be conducted, thus reducing the overall number of ferrets used.		
ECBS outcome	[BLANK]		

Proposal (title)	**3rd International Standard for anti-rabies immunoglobulin, human**		
Proposer (name of Institution)	NIBSC	**Principal contact**	Dianna Wilkinson
Rationale	Replacement. Stocks of the 2nd IS is nearing depletion and has been placed under restricted sales.		
Anticipated uses and users	Standardisation of assays for the detection and quantification of rabies antibodies. Rabies antibody assays are used to evaluate the immunogenicity of human rabies vaccines and the potency of immunoglobulins for post-exposure prophylaxis.		
Source/type of materials	Human Immunoglubulin Preparations. Requires donation(s) from manufacturers.		
Outline of proposed collaborative study	The aim of the collaborative study is to calibrate the candidate IS in International Units against the 2nd IS in assays such as: • rapid fluorescent focus inhibition test (RFFIT), which measures the neutralisation activity of RIG against the rabies challenge virus standard 11 (CVS-11). • mouse neutralization test (MNT) and the plaque reduction assay. (used less ofter than RFFIT). • CVS-11 (G protein) pseudotyped lentiviral particle neutralisation assay. Currently undergoing a feasibility study for adoption into the European Pharmacopoeia. The collaborative study will involve 6-12 laboratories worldwide, performing a range of Rabies vaccine assays, and representing manufacturers of rabies vaccines and control labs. Study samples will include the candidate replacement standard, the 2nd IS and, if possible, the EDQM reference material.		
Issues raised by the proposal	Availability or ability of manufacturers to donate the IgG is uncertain. The current IS may become depleted before its replacement is established.		
Action required	ECBS to endorse proposal		
Proposer's project reference		**Date proposed:**	18/06/2017
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method			
Number of products or methods	Several		
Public health importance	Rabies is a neglected zoonosis with a substantial public health and economic impact.		
Global importance	~60 000 people die of rabies every year, mostly in Asia and Africa. In more than 99% of all cases of human rabies, the virus is transmitted via dogs; half of the global population lives in canine rabies-endemic areas and is considered at risk for contracting rabies WHO supports targets for elimination of human and dog rabies in all Latin American countries by 2015 and of human rabies transmitted by dogs in South-East Asia by 2020.		
Global need from regulatory & scientific	Many national regulatory requirements for assay of rabies IgG potency state that it is necessary to include in the assay of a reference preparation of rabies IgG		

considerations	(calibrated in International Units).
ECBS outcome	

Proposal:	**Erythromycin, 3rd IS**		
Proposer:	European Directorate for the Quality of Medicines & HealthCare (EDQM) Department of Biological Standardisation, OMCL Network & HealthCare (DBO) 7 allée Kastner CS 30026 F-67081 Strasbourg France	**Principal Contact**	Karl-Heinz Buchheit, Head DBO (karl.buchheit@edqm.eu, Tel: +33 3 90 21 48 55) Sally Woodward, Assistant (sally.woodward@edqm.eu, Tel: +33 3 90 21 50 48)
Rationale:	Replacement of current lot due to low stocks		
Anticipated Uses and Users:	International Standard used by Pharmacopoeias, National / Regional Authorities to establish their secondary standards and by manufacturers to establish their in-house standards where appropriate		
Source/Type of Materials:	Bulk material obtained from a major manufacturer will be suitably formulated and processed by EDQM		
Outline of proposed collaborative study	A collaborative study which will involve Pharmacopoeias, national control laboratories and manufacturer, followed by an appropriate statistical evaluation taking the current IS as the primary standard. About 12 participants from different regions of the world are envisaged.		
Issues raised by the proposal:	None		
Action required:	Approval by ECBS		
Study Ref:		**Date proposed:**	28 April 2017
ECBS Outcome:			
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	Erythromycin is used globally as antibiotic and listed by WHO as Essential Medicine.		

Number of products or methods	Numerous products, all over the world
Public health importance	High
Global importance	High
Global need from regulatory & scientific considerations	The 3rd IS for Erythromycin will be needed for the calibration of regional, national and in-house standards in order to guarantee appropriate filling and dosing of erythromycin preparations. Thus there is a global need for this standard.
ECBS outcome	