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Geneva, 17 to 21 October 2011**

Requests to initiate new WHO reference material projects for vaccines and related substances; for cytokines, growth factors and endocrinological substances; and for antibiotics

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 14 October 2010 and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Quality Safety and Standards (QSS). Comments may also be submitted electronically to the Responsible Officer: Dr David Wood (woodd@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 materials and standards 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/11.2177) cover requests to initiate new projects in the areas of (a) vaccines and related substances, (b) cytokines, growth factors and endocrinological substances, and (c) antibiotics.

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Appendix 1 Vaccines and related substances

Antibody to Pandemic Influenza H1N1 Virus

Proposal (title)	The second International Standard for antibody to pandemic H1N1 influenza virus		
Proposer (name of Institution)	NIBSC	Principal contact	Diane Major
Rationale	Stock levels of the first International Standard for antibody to pandemic H1N1 influenza virus are low and not expected to fulfill future demand		
Anticipated uses and users	Serology for vaccine trials and serum surveys Vaccine manufacturers; independent serology labs; clinical labs, and national control laboratories		
Source/type of materials	Human plasma from recipients of H1N1pdm vaccine		
Outline of proposed collaborative study	Assays of candidate IS, first IS and test sera in 20 laboratories worldwide		
Issues raised by the proposal	Will the candidate IS reduce assay variability to a similar extent as the first IS? Will the assigned unitage be similar to that of the first IS?		
Action required	ECBS to endorse proposal		
Proposer's project reference	VIR00021	Date proposed:	April 2011
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	H1N1 pdm is included in trivalent influenza vaccines which are licensed and in use		
Number of products or methods	Numerous vaccines worldwide		
Public health importance	Influenza is given public health importance in most countries		
Global importance	Globally important as the H1N1pdm virus is still circulating		
Global need from regulatory & scientific considerations	It is very difficult to compare different vaccines due to variability in serology assays. This has scientific and regulatory significance		
ECBS outcome			

Appendix 2 Cytokines, growth factors and endocrinological substances

IL-2

Proposal (title)	Proposed WHO 2 nd IS for human Interleukin-2 (IL-2)		
Proposer (name of Institution)	NIBSC	Principal contact	Meenu Wadhwa
Rationale	The current WHO 1 st IS (coded 86/504; 100 IU/ampoule) for Interleukin-2 (IL-2) is used for the potency labelling of IL-2 products approved for the treatment of metastatic renal cell carcinoma and metastatic melanoma patients. Additionally, based on its ability to induce proliferation of CD4 ⁺ cells, it has been clinically tested in HIV positive patients either alone or as combination therapy with antiviral agents. Based on promising results from preliminary studies using combination therapy, further clinical trials are ongoing in HIV +ve patients. Stocks of the 1 st IS will be near exhaustion in 2014 and a replacement is required.		
Anticipated uses and users	This will be used by manufacturers and regulatory authorities for potency estimation of therapeutic IL-2 products. 100 -150 ampoules of the 1 st IS (native, cell-derived) per year are dispatched. Current stock ~ 800 ampoules.		
Source/type of materials	rDNA derived human IL-2 (coded 86/564 - from the previous collaborative study; assigned unitage of 202 IU/ampoule). Current stocks ~1900 ampoules ; ~ 100 ampoules distributed yearly		
Outline of proposed collaborative study	The proposed multi-centre international study will include evaluation of two candidate preparations (from the previous collaborative study) predominantly using bioassays; the unitage will be assigned relative to the current IS. One of the candidate rDNA derived human IL-2 (coded 86/564) preparations from the previous collaborative study is currently distributed with no reported issues. Limited stability studies after 22 years of lyophilization have indicated no loss of biological activity.		
Issues raised by the proposal	A stock (500 ampoules) of 1 st IS, natural sequence human cell derived IL-2 will need preserving as we will not be able to procure this again.		
Action required	ECBS to endorse proposal		
Proposer's project reference	BIO 00047	Date proposed:	Feb 2011
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	Licensed product		
Number of products or methods	1 licensed in USA, Europe & Canada, others in China, India, Latin American countries and elsewhere; cell-derived multi-component as well as gene therapy based products in clinical trials.		

Public health importance	Yes
Global importance	Yes
Global need from regulatory & scientific considerations	Yes
ECBS outcome	

Erythropoietin

Proposal (title)	Proposed 3 rd International Standard for Erythropoietin, recombinant for bioassay		
Proposer (name of Institution)	NIBSC	Principal contact	Chris Burns
Rationale	Stocks of the current IS for recombinant human erythropoietin (rhuEPO) for bioassay are running low and there is a requirement for a new International Standard for the potency measurement of preparations of rhuEPO by in vivo bioassay.		
Anticipated uses and users	300/400 ampoules per year. Used by manufacturers of EPO therapeutic products, regulatory and quality assurance bodies.		
Source/type of materials	Recombinant EPO supplied by manufacturer(s).		
Outline of proposed collaborative study	Participants would be asked to calibrate the candidate standard in terms of the 2 nd IS by polycythaemic or normocythaemic mouse bioassay. Confirmatory data would be requested from physico-chemical analyses.		
Issues raised	None		
Action required	ECBS to endorse proposal		
Proposer's reference	N/A	Date proposed:	March 2010
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	EPO is licensed globally.		
Number of products or methods	4 or 5 major EPO products and an increasing number of manufacturers bringing biosimilar EPOs to the market.		
Public health importance	The International Standard defines the IU for EPO activity and is essential for the correct potency labeling of therapeutic EPO products used to treat anemia in end-stage renal disease and anemia associated with cancer and other diseases.		

Global importance	EPO is used globally as a therapeutic product for the treatment of anemia.
Global need from regulatory & scientific considerations	The International Standard defines the IU for EPO activity and is essential to enable manufacturers to correctly assign a potency to their therapeutic products.
ECBS outcome	

FSH/LH

Proposal (title)	The proposed 5th International Standard for Urinary Follicle Stimulating Hormone (FSH) and Urinary Luteinizing Hormone (LH)		
Proposer	NIBSC	Principal contact	Jackie Ferguson
Rationale	Stocks of the 4th International Standard, 98/704, are nearly exhausted and there is an urgent requirement to prepare a replacement. 450 ampoules are dispatched worldwide/yr.		
Anticipated uses and users	The International Standard defines the IU for Urinary FSH/LH activity and is essential for the correct potency labelling of therapeutic preparations of urinary FSH/LH (menotrophin) used to treat anovulation in women and hypo- or normo- gonadotrophic hypogonadism in men. It is also used for ovarian hyperstimulation for assisted reproductive technologies (ART).		
Source/type of materials	Highly purified urinary FSH/LH has been donated by Institut Massone S. A., Argentina and Institut Biochimique S. A. (IBSA), Switzerland.		
Outline of proposed collaborative study	Participants would be asked to calibrate the standard in terms of the 4 th IS by rat ovarian weight gain (FSH) and immature rat seminal vesicle weight gain (LH) bioassays. Confirmatory data would be requested by in vitro bioassay.		
Issues raised by the proposal	No issues raised. Stocks of 98/704 are running low and customer's orders are now restricted.		
Action required	Endorsement by WHO		
Project reference	BIO-00032	Date proposed:	18.01.2011
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	The medicine is approved for the conditions stated above.		
Number of products or methods	There are >15 branded products available including highly purified preparations. Increased marketing of biosimilar preparations is anticipated due to patent expiry.		
Public health importance	Urinary FSH/LH preparations continue to be used to treat the above conditions. The approval of highly purified preparations which are considered cost effective, well tolerated and comparable to recombinant products has extended the use of urinary-derived gonadotropins.		

Global importance	Urinary FSH/LH products are manufactured and marketed worldwide. The demand for low cost preparations, particularly for ART in countries where it is not funded by government or healthcare plans necessitates effective standardization.
Global need from regulatory & scientific considerations	The continued provision of branded urinary FSH/LH products and the entry into the market of biosimilar preparations requires the replacement of the fourth IS, 98/704.
ECBS outcome	

LH

Proposal (title)	Proposed 3 rd International Standard for Luteinizing Hormone, Human, Pituitary		
Proposer (name of Institution)	NIBSC	Principal contact	Chris Burns
Rationale	Stocks of the current IS for Luteinizing Hormone, Human, Pituitary are running low and there is a requirement for a replacement International Standard for the calibration of Luteinizing Hormone (LH) immunoassays. Measurements of LH are used in the diagnosis of hypothalamic, pituitary, or gonadal dysfunction. In addition, LH levels are used to determine menopause, pinpoint ovulation, and monitor endocrine therapy.		
Anticipated uses and users	150/200 ampoules per year. Used by manufacturers LH assays, regulatory and quality assurance bodies.		
Source/type of materials	A batch of 3000 ampoules (prepared in the same way as the 2 nd IS from the same starting LH preparation) has already been filled and is coded 81/535.		
Outline of proposed collaborative study	The candidate IS would be value-assigned against the 2 nd IS using current commercial immunoassay methods.		
Issues raised by the proposal	None		
Action required	ECBS to endorse proposal		
Proposer's project reference	N/A	Date proposed:	April 2011
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	Licensed LH immunoassays are an established component of the battery of clinical endocrinology tests used in the diagnosis of a range of diseases.		
Number of products or methods	More than 20 licensed LH immunoassays		
Public health	Immunoassays of LH in human plasma have many important applications		

importance	in clinical medicine and reproductive physiology
Global importance	LH is measured globally.
Global need from regulatory & scientific considerations	It is essential that there be a continued provision of an International Standard for LH to ensure the comparability of LH results and the correct application of clinical practice guidelines.
ECBS outcome	

Appendix 3 Antibiotics

Neomycin B

Proposal (title)	The second International Standard for Neomycin B		
Proposer (name of Institution)	EDQM	Principal contact	Karl-Heinz Buchheit
Rationale	Replacement of First IS for Neomycin B, the stocks of which will be depleted in 2012-2013		
Anticipated uses and users	Antibiotic; the IS is and will be used for the microbiological assay during the quality control of the antibiotic by manufacturers and public control laboratories		
Source/type of materials	Bulk material obtained from one manufacturer of Neomycin B; final presentation: freeze-dried		
Outline of proposed collaborative study	Manufacturers and public control laboratories from all over the world will be invited to participate. Five to 15 participants are expected to participate.		
Issues raised by the proposal	None		
Action required	ECBS to endorse proposal		
Proposer's project reference	ISA012	Date proposed:	June 2011
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	Neomycin B is a marketed antibiotic		
Number of products or methods	numerous		
Public health importance	High; need for batch control of Neomycin B		
Global importance	High; Neomycin B is used globally		
Global need from regulatory & scientific considerations	High; see above		
ECBS outcome			

Neomycin

Proposal (title)	The third International Standard for Neomycin		
Proposer (name of Institution)	EDQM	Principal contact	Karl-Heinz Buchheit
Rationale	Replacement of Second IS for Neomycin, the stocks of which will be depleted in 2012-2013		
Anticipated uses and users	Antibiotic; the IS is and will be used for the microbiological assay during the quality control of the antibiotic by manufacturers and public control laboratories		
Source/type of materials	Bulk material obtained from one manufacturer of Neomycin; final presentation: freeze-dried		
Outline of proposed collaborative study	Manufacturers and public control laboratories from all over the world will be invited to participate. Five to 15 participants are expected to participate.		
Issues raised by the proposal	None		
Action required	ECBS to endorse proposal		
Proposer's project reference	ISA011	Date proposed:	June 2011
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	Neomycin is a marketed antibiotic		
Number of products or methods	numerous		
Public health importance	High; need for batch control of Neomycin		
Global importance	High; Neomycin is used globally		
Global need from regulatory & scientific considerations	High; see above		
ECBS outcome			