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WHO manual for the establishment of national and other secondary standards for vaccines

Immunization, Vaccines and Biologicals

World Health Organization

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World Health Organization
Department of Immunization, Vaccines and Biologicals
CH-1211 Geneva 27, Switzerland
• *Fax:* + 41 22 791 4227 • *Email:* vaccines@who.int •

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Preface

The World Health Organization through its Expert Committee on Biological Standardization (ECBS) developed the Recommendations for the preparation, characterization and establishment of international and other biological reference standards in 1978. This document was last revised in 2004 and is available in the WHO Technical Report Series 932 and its website (http://whqlibdoc.who.int/trs/WHO_TRS_932_eng.pdf).

Feedback from the National Control Laboratories (NCLs) and vaccine manufacturers indicated that they had many questions concerning the characterization, calibration and establishment of national or regional standards or working standards. A practical manual for the use by the NCLs and vaccine manufacturers would be of help, as would training in an experienced laboratory. ECBS had agreed that the calibration of a secondary reference is a complex process and more extensive guidance is required. Issues that had been identified were traceability, compliance with regulatory requirements, uncertainty value, if applicable, restrictions of the range of assay methods and the availability of a large data set to reduce uncertainty, the evaluation of stability and a monitoring program against the International Standard (IS).

The development of a manual to provide technical assistance for staff at the NCLs and vaccine manufacturers had been discussed with senior scientists at the National Institute for Biological Standards and Control, UK in April 2006 and scientists had developed the first draft in December 2006. This draft manual had been circulated for comment and was reviewed in a consultation in 2007 in Geneva at which improvements and modifications were proposed and incorporated into the document. This version was finalized by Dr Morag Ferguson National Institute for Biological Standards and Control, UK and Dr Dianliang Lei, Quality, Safety and Standards Team, Immunizations, Vaccines and Biologicals Department, World Health Organization, based on the comments received from NCLs and Vaccine Industry. Appendices containing additional guidance on the process have been added along with examples of collaborative studies on International Standards for the reference of readers when they calibrate their secondary standards.

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Dr Dorothy Xing, National Institute for Biological Standards and Control, UK for preparing and providing an example on a collaborative study to evaluate a candidate replacement international standard for whole cell pertussis vaccine.

Dr Thea Sesardic and Dr Paul Stickings, National Institute for Biological Standards and Control, UK for preparing and providing an example of Calibration of a Reference Preparation for Diphtheria Vaccine (Adsorbed) and an example of calibration study to replace international standard for Tetanus Toxoid for use in flocculation test.

Dr Morag Ferguson National Institute for Biological Standards and Control, UK for preparing and preparing examples of a collaborative study to calibrate a candidate standard for rabies vaccine and a collaborative study on calibration of a standard for yellow fever vaccine.

Glossary

Definitions from the Recommendations for the Preparation, Characterization and Establishment of International and other Biological Reference Standards

Baseline samples. Samples that are retained under optimal storage conditions to retain biological or immunological activity and that are used for comparison purposes. The baseline samples will need to be stored at a lower temperature than the storage temperature used for the established reference preparation. This is not appropriate for adjuvanted vaccines

Biologicals are "substances which cannot be fully characterized by physico-chemical means alone, and which therefore require the use of some form of bioassay".

Biological tests (bioassay). A biological test is a laboratory procedure for the estimation of the nature or potency of a material by means of the reaction that follows its application to some elements of a living system (examples include animals , tissues, cells, receptors and enzymes). The potency of the material being measured is often defined in International Units or, in some circumstances, may be defined in terms of International System of Units (SI), by comparison with the reaction of the system to a biological reference preparation

An *immunological* test is a procedure that requires the use of antigens and/or antibodies to measure the analyte in a biological product or sample.

A *calibrant* is a substance used in chemical analysis to calibrate the response of a measurement system to the analyte

A *calibrator* is a material that is used to adjust instrumentation that is based on or traceable to a reference preparation