

W H O T e c h n i c a l R e p o r t S e r i e s  
9 9 3

# WHO Expert Committee on Biological Standardization

---

Sixty-fifth report

*This report contains the collective views of an international group of experts and  
does not necessarily represent the decisions or the stated policy of the World Health Organization*



**World Health  
Organization**

WHO Library Cataloguing-in-Publication Data:

WHO Expert Committee on Biological Standardization, sixty-fifth report.

(WHO technical report series ; no. 993)

1. Biological Products - standards. 2. Vaccines - standards. 3. Blood - standards.  
4. Anti-Bacterial Agents - standards. 5. Reference Standards. 6. Diagnostic Test Approval.  
I. World Health Organization. II. WHO Expert Committee on Biological Standardization  
(2014: Geneva, Switzerland). III. Series.

ISBN 978 92 4 120993 9

(NLM classification: QW 800)

ISBN (PDF) 978 92 4 069409 5

ISSN 0512-3054

© World Health Organization 2015

All rights reserved. Publications of the World Health Organization are available on the WHO website ([www.who.int](http://www.who.int)) or can be purchased from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: [bookorders@who.int](mailto:bookorders@who.int)).

Requests for permission to reproduce or translate WHO publications –whether for sale or for non-commercial distribution – should be addressed to WHO Press through the WHO website ([www.who.int/about/licensing/copyright\\_form/en/index.html](http://www.who.int/about/licensing/copyright_form/en/index.html)).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This publication contains the collective views of an international group of experts and does not necessarily represent the decisions or the policies of the World Health Organization.

**Printed in Italy**

# Contents

<b>Abbreviations</b>	xiii
<b>1. Introduction</b>	1
<b>2. General</b>	4
2.1 Current directions	4
2.1.1 Strategic directions in biological standardization: WHO priorities	4
2.1.2 Vaccines and biotherapeutics: recent and planned activities in biological standardization	5
2.1.3 Therapeutic biological medicines: current developments and challenges	7
2.1.4 Blood products and related in vitro diagnostics: recent and planned activities in biological standardization	8
2.1.5 Overview of the international response to the Ebola epidemic, including accelerated development of vaccines and novel therapies	10
2.2 Reports	11
2.2.1 Report from the WHO Blood Regulators Network	11
2.2.2 Report from the WHO collaborating centres for biological standards	13
2.3 Feedback from custodian laboratories	14
2.3.1 Developments and scientific issues highlighted by custodians of WHO biological reference preparations	14
2.4 Cross-cutting activities of other WHO committees and groups	17
2.4.1 Proposed WHO Guidelines on good review practices	17
2.4.2 Proposed technical supplements to WHO guidance on the storage and transport of time- and temperature-sensitive pharmaceutical products	18
2.4.3 Proposed WHO Guidelines on good regulatory practices	18
2.4.4 Collaborative procedure for facilitating the licensing of WHO-prequalified medicinal products	19
2.4.5 Update of matters arising from the Expert Group on International Nonproprietary Names	19
2.4.6 Proposal to revise the procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies	20
2.4.7 A WHO and EDQM collaborative study on the determination of saccharide content of the <i>Haemophilus influenzae</i> type b component in liquid vaccine presentations	21
2.4.8 Update on the WHO global action plan to minimize poliovirus facility-associated risk	21
<b>3. International Recommendations, Guidelines and other matters related to the manufacture and quality control of biological substances</b>	23
3.1 Vaccines and related substances	23
3.1.1 Scientific principles for regulatory risk evaluation on finding an adventitious agent in a marketed vaccine	23
3.1.2 Recommendation to assure the quality, safety and efficacy of poliomyelitis vaccines (inactivated)	24
3.1.3 Guidelines on procedures and data requirements for changes to approved vaccines	25
3.1.4 Regulatory written standards pipeline	26

3.1.5	Clinical evaluation of dengue vaccines	27
3.1.6	Biotherapeutic products including similar biotherapeutic products	27
3.1.7	Multilateral activities relating to biotherapeutic products including similar biotherapeutic products	28
3.2	Blood products and related substances	28
3.2.1	Strengthening production capacity for blood components including plasma for fractionation	28
3.2.2	Shortage of anti-diphtheria and other specific immunoglobulins	30
3.2.3	MERS coronavirus serum panel	30
3.2.4	Use of convalescent sera to respond to emerging infectious disease threats	31
3.2.5	Overview of the biological standards endorsed by the ISTH for WHO approval	32
<b>4.</b>	<b>International reference materials – antibiotics</b>	<b>33</b>
4.1	WHO International Standards and Reference Reagents – antibiotics	33
4.1.1	Second WHO International Standard for bleomycin complex A2/B2	33
4.2	Proposed new projects and updates – antibiotics	33
4.2.1	Proposed Third WHO International Standard for amphotericin B	33
<b>5.</b>	<b>International reference materials – biotherapeutics other than blood products</b>	<b>35</b>
5.1	WHO International Standards and Reference Reagents – biotherapeutics other than blood products	35
5.1.1	Third WHO International Standard for luteinizing hormone (human pituitary)	35
5.1.2	First WHO International Standard for proinsulin (human)	36
5.2	Proposed new projects and updates – biotherapeutics other than blood products	36
5.2.1	Proposed First WHO Reference Reagent for Rituximab for use in complement-dependent cytotoxicity assays	36
5.2.2	Proposed First WHO Reference Reagent for Batroxobin	37
<b>6.</b>	<b>International reference materials – blood products and related substances</b>	<b>39</b>
6.1	WHO International Standards and Reference Reagents – blood products and related substances	39
6.1.1	First WHO International Standard for activated blood coagulation factor XI	39
6.1.2	First WHO Reference Panel for lupus anticoagulant	40
6.1.3	First WHO International Standard for A Disintegrin And Metalloprotease with ThromboSpondin type 1 motifs 13 (ADAMTS13)	41
6.1.4	Fourth WHO International Standard for plasmin	41
6.2	Proposed new projects and updates – blood products and related substances	42
6.2.1	Proposed Second WHO International Standard for blood coagulation factor XI	42
6.2.2	Proposed Second WHO International Standard for activated blood coagulation factor IX	43
6.2.3	Proposed second WHO reference reagents for anti-A and anti-B in intravenous immunoglobulin	43
<b>7.</b>	<b>International reference materials – In vitro diagnostic device reagents</b>	<b>44</b>
7.1	WHO International Standards and Reference Reagents – in vitro diagnostic device reagents	44
7.1.1	Third WHO International Standard for hepatitis B virus surface antigen	44

7.1.2	First WHO International Standard for <i>Toxoplasma gondii</i> DNA for NAT-based assays	45
7.1.3	First WHO International Standard for hepatitis C virus core antigen	45
7.2	Proposed new projects and updates – in vitro diagnostic device reagents	46
7.2.1	Proposed First WHO Reference Panel for vCJD	46
7.2.2	Proposed first WHO international standards for herpes simplex virus DNA type 1 and 2	47
7.2.3	Proposed replacement WHO international standards for prostate-specific antigen (free) and prostate-specific antigen (90:10)	48
7.2.4	Proposed First WHO International Standard for anti-Müllerian hormone	48
7.2.5	Proposal to assign a holotranscobalamin value to the First WHO International Standard for vitamin B12 and folate in human serum	49
<b>8.</b>	<b>International reference materials – vaccines and related substances</b>	<b>50</b>
8.1	WHO International Standards and Reference Reagents – vaccines and related substances	50
8.1.1	First WHO Reference Reagent for anti-malaria ( <i>Plasmodium falciparum</i> ) human serum	50
8.1.2	Second WHO International Standard for <i>Haemophilus influenzae</i> type b capsular polysaccharide	51
8.1.3	First WHO International Standard for anti-typhoid capsular Vi polysaccharide immunoglobulin G (human)	52
8.2	Proposed new projects and updates – vaccines and related substances	53
8.2.1	Proposed Second WHO International Standard for <i>Bordetella pertussis</i> toxin	53
8.2.2	Proposed Third WHO International Standard for tetanus toxoid for use in flocculation test	54
8.2.3	Proposed Seventh WHO International Standard for rabies vaccine	55
8.2.4	Proposed First WHO International Standard for meningococcal serogroup X polysaccharide	55
8.2.5	Proposed First WHO International Standard for antibody to A(H7N9) influenza virus	56
<b>Annex 1</b>		
	WHO Recommendations, Guidelines and other documents related to the manufacture and quality control of biological substances used in medicine	57
<b>Annex 2</b>		
	Scientific principles for regulatory risk evaluation on finding an adventitious agent in a marketed vaccine	63
<b>Annex 3</b>		
	Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (inactivated)	
	Replacement of Annex 2 of WHO Technical Report Series, No. 910	89
<b>Annex 4</b>		
	Guidelines on procedures and data requirements for changes to approved vaccines	175
<b>Annex 5</b>		
	Biological substances: WHO International Standards, Reference Reagents and Reference Panels	261

## WHO Expert Committee on Biological Standardization

13 to 17 October 2014

### Committee members<sup>1</sup>

Professor K. Cichutek, Paul-Ehrlich-Institut, Langen, Germany

Dr J. Epstein, Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD, United States of America (USA) (*also Blood Regulators Network (BRN) representative*)

Dr E. Griffiths, Kingston-upon-Thames, England (*Chairman*)

Dr S. Hindawi, Blood Transfusion Services, Jeddah, Saudi Arabia

Mrs T. Jivapaisarnpong, Institute of Biological Products, Ministry of Public Health, Nonthaburi, Thailand

Dr H. Klein, National Institutes of Health, Bethesda, MD, USA (*Vice Chairman*)

Dr P. Minor, National Institute for Biological Standards and Control, Potters Bar, England

Dr J. Petricciani, Palm Springs, CA, USA (*Rapporteur*)

Mr V.R. Reddy,<sup>2</sup> South African National Blood Service, Weltevreden Park, South Africa

Dr L.S. Slamet, Technical Adviser and Consultant to the National Agency of Drug and Food Control, Jakarta, Indonesia

Dr Y. Sohn, Ministry of Food and Drug Safety, Chungcheongbuk-do, Republic of Korea

Dr J. Wang, National Institutes for Food and Drug Control, Beijing, China

Professor H. Yin,<sup>2</sup> China Food and Drug Administration, Beijing, China

Dr K. Zoon, National Institutes of Health, Bethesda, MD, USA

### Representatives of other organizations

*Advanced Medical Technology Association*

Dr R. Enns, Consultant to Cepheid, Sunnyvale, CA, USA

*Bill & Melinda Gates Foundation*

Dr N. Wairagkar, Bill & Melinda Gates Foundation, Seattle, WA, USA

<sup>1</sup> The decisions of the Committee were taken in closed session with only members of the Committee present. Each Committee member had completed a Declaration of Interests form prior to the meeting. These were assessed by the WHO Secretariat and no declared interests were considered to be in conflict with full meeting participation.

<sup>2</sup> Unable to attend.

*Council of Europe, European Directorate for the Quality of Medicines & HealthCare*

Dr K-H. Buchheit, Official Medicines Control Laboratories Network and HealthCare,  
Strasbourg, France

Dr E. Charton, European Pharmacopoeia Department, Strasbourg, France

*Developing Country Vaccine Manufacturers Network<sup>3</sup>*

Dr S. Gairola, Serum Institute of India Ltd., Pune, India

Dr V. Paradkar, Biological E. Limited, Hyderabad, India

*International Federation of Clinical Chemistry and Laboratory Medicine*

Professor P. Gillery, American Memorial Hospital, Reims, France

*International Federation of Pharmaceutical Manufacturers & Associations<sup>3</sup>*

D. Colette, GlaxoSmithKline Vaccines, Wavre, Belgium

Dr C. Saille, GlaxoSmithKline Vaccines, Wavre, Belgium

Dr M. English,<sup>4</sup> Merck, West Point, PA, USA

Mr M. McGoldrick,<sup>4</sup> Merck, West Point, PA, USA

Dr D. Schmalzing,<sup>4</sup> Merck, West Point, PA, USA

Dr S. Pluschke, Pfizer Inc., Groton, CT, USA

Dr L. Mallet, Sanofi Pasteur, Marcy L'Etoile, France

*International Generic Pharmaceuticals Alliance*

Dr S. Kox, European Generic Medicines Association, Brussels, Belgium

*International Plasma Fractionation Association*

Dr P. Strengers, Amsterdam, Netherlands

*International Society of Blood Transfusion*

Dr C. Bianco, Amsterdam, Netherlands

*International Society on Thrombosis and Haemostasis*

Dr P. Lenting, Le Kremlin-Bicêtre, France

*Pharmaceutical and Medical Device Regulatory Science Society of Japan*

Dr T. Murai, Osaka, Japan

*Plasma Protein Therapeutics Association*

Dr I. von Hoegen, Brussels, Belgium

*United States Pharmacopeial Convention*

Dr F. Atouf, Rockville, MD, USA

<sup>3</sup> A maximum of two representatives of the DCVMN and two representatives of the IFPMA were present in the meeting room during discussion of any one agenda item.

<sup>4</sup> Participated via teleconference.

*United States Pharmacopeial Convention—India*

Dr R. Chakrabarti, Hyderabad, India

### Temporary advisers

Ms S. Boucher, Bacterial and Combination Vaccines Division, Health Canada, Ottawa, Ontario, Canada

Dr K. Chumakov,<sup>5</sup> Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD, USA

Dr C. Conrad, Paul-Ehrlich-Institut, Langen, Germany

Dr S. Gagneten,<sup>5</sup> Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD, USA

Dr A. Hubbard, National Institute for Biological Standards and Control, Potters Bar, England  
(*Rapporteur for the blood products and in vitro diagnostics track*)

Dr M. Lennon, Horning, England

Dr H. Meyer, Paul-Ehrlich-Institut, Langen, Germany

Dr M. Nübling, Paul-Ehrlich-Institut, Langen, Germany (*Rapporteur for the blood products and in vitro diagnostics track*)

Dr A. Padilla, Madrid, Spain (*Lead for the blood products and in vitro diagnostics track*)

Dr R. Sheets, Silver Spring, MD, USA

Dr A.L. Waddell, Stanley, England

Mr M. Welin, Medical Products Agency, Uppsala, Sweden

Dr T. Wu, Bacterial and Combination Vaccines Division, Health Canada, Ottawa, Ontario, Canada

### Participants

Dr F. Agbanyo, Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Ontario, Canada (*also BRN representative*)

993, 2015

预览已结束，完整报告链接和二维码如下：

[https://www.yunbaogao.cn/report/index/report?reportId=5\\_27583](https://www.yunbaogao.cn/report/index/report?reportId=5_27583)

