WHO Technical Report Series
897

WHO EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Forty-ninth Report

World Health Organization
Geneva 2000

WHO Library Cataloguing-in-Publication Data

WHO Expert Committee on Biological Standardization (1998 : Geneva, Switzerland)
WHO Expert Committee on Biological Standardization : forty-ninth report

(WHO technical report series ; 897)

1.Biological products – standards 2.Guidelines I.Title II.Series

ISBN 92 4 120897 X (NLM Classification: QW 800)
ISSN 0512-3054

Printed in Switzerland

2000/13266 – Stratcom/Schuler — 6500

Contents

Introduction 1

General 2
Developments in biological standardization 2
Global project on quality assurance of plasma-derived medicinal products and plasma-fractionation activities 3
Independent review of WHO's remit and activities in the field of biologicals 3
Reverse transcriptase associated with avian cells 5
Comments from users of recommendations (requirements) and guidelines published by WHO and international reference materials 6
International nonproprietary names 7

International guidelines, recommendations and other matters related to the manufacture and quality control of biologicals 7
Recommendations for *Haemophilus influenzae* type b conjugate vaccine 7
Recommendations for poliomyelitis vaccine (oral) 8
Guidelines for the production and control of the acellular pertussis component of monovalent or combined vaccines 9
List of recommendations for biological substances and other sets of recommendations: proposed new format, electronic publication and proposed discontinuations 11
Work in progress and proposed new work on recommendations and guidelines 12

International reference materials 13
Review of existing reference materials: proposed database and electronic publication 13
Proposals for replacement or discontinuation 14
Work in progress and proposed new work: general report 16
WHO consultation on review and replacement of International Standards for blood-grouping reagents 17
Working group on reference preparations for testing diagnostic kits used for detection of hepatitis B and C and human immunodeficiency virus in blood screening 17
Standardization of diagnostic tests for prions 18

Antibodies 19
Clostridium perfringens beta antitoxin, equine 19
Anti-hepatitis A immunoglobulin and serum, human 19

Antigens and related substances 19
Pertussis vaccine: third International Standard 19

Blood products and related substances 20
Blood coagulation factor VII concentrate 20
Blood coagulation factor VIII concentrate 21
Blood coagulation factor VIII and von Willebrand factor in plasma 21
Blood coagulation factor IXa, human 21
Haemoglobincyanide 22

WHO informal consultation on standardization of unfractionated heparin and proposed fifth International Standard for Unfractionated Heparin 22
Plasmin 23

Cytokines 23
WHO informal consultation on cytokine standards 23
Activin A, human, recombinant 24
Interleukin-2 soluble receptor 24
Sex hormone binding globulin 25

Miscellaneous 25
Botulinum type A toxin 25

Annex 1
Recommendations for the production and control of *Haemophilus influenzae* type b conjugate vaccines 27

Annex 2
1990 Requirements for poliomyelitis vaccine (oral) (Addendum 1998) 61

Annex 3
Recommendations and guidelines for biological substances used in medicine and other documents 67

Annex 4
International Biological Reference Preparations 71

Annex 5
Biological substances: International Standards and Reference Reagents 101

Annex 6
Corrigendum: International Standard for Insulin-like Growth Factor 1 103

WHO Expert Committee on Biological Standardization

Geneva, 19–23 October 1998

Members

Dr D. Calam, European Coordinator, National Institute for Biological Standards and Control, WHO International Laboratory for Biological Standards, Potters Bar, Herts., England

Dr M. de los Angeles Cortés Castillo, Subdirector, Quality Control, National Institute of Hygiene, Mexico City, Mexico

Dr R. Dobbelaer, Head, Biological Standardization, Louis Pasteur Scientific Institute of Public Health, Brussels, Belgium

Dr V. Grachev, Deputy Director, Institute of Poliomyelitis and Viral Encephalitides, Moscow, Russian Federation

Dr J.G. Kreeftenberg, Bureau for International Cooperation, National Institute of Public Health and Environmental Protection, Bilthoven, Netherlands (*Vice-Chairman*)

Dr F.A. Ofosu, Department of Pathology, McMaster University, Hamilton, Ontario, Canada

Dr Zhou Hai-jun, Director, National Institute for the Control of Pharmaceutical and Biological Products, Temple of Heaven, Beijing, China

Dr K. Zoon, Director, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD, USA (*Chairwoman*)

Representatives of other organizations

Council of Europe
Mr J.-M. Spieser, Head, Biological Standardization, European Department for the Quality of Medicines, Council of Europe, Strasbourg, France

European Association of the Plasma Products Industry
Dr I. von Hoegen, Director, Regulatory Affairs, Brussels, Belgium

International Association of Biological Standardization
Professor F. Horaud, Pasteur Institute, Paris, France

International Federation of Pharmaceutical Manufacturers Associations
Dr M. Duchêne, Director, Quality Control and Regulatory Affairs, SmithKline Beecham Biologicals, Rixensart, Belgium

Dr J.-C. Vincent-Falquet, Director, Regulatory Affairs, Pasteur Mérieux Connaught, Marcy l'Etoile, France

International Society of Blood Transfusion
Dr M.L. Scott, International Blood Group Reference Laboratory, Bristol, England

International Society on Thrombosis and Haemostasis
Dr D. Thomas, Kirtlington, Oxford, England

Secretariat

Dr Y. Arakawa, Director, Department of Bacterial and Blood Products, National Institute of Infectious Diseases, Tokyo, Japan (*Temporary Adviser*)

Dr D. Armstrong, Executive Director, Natal Bioproducts Institute, Pinetown, South Africa (*Temporary Adviser*)

Dr T. Barrowcliffe, National Institute for Biological Standards and Control, WHO International Laboratory for Biological Standards, Potters Bar, Herts., England (*Temporary Adviser*)

Dr E. Griffiths, Chief, Biologicals, World Health Organization, Geneva, Switzerland

Dr M.C. Hardegree, Director, Office of Vaccine Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD, USA (*Temporary Adviser*)

Dr A.M. Padilla, Scientist, Biologicals, World Health Organization, Geneva, Switzerland

Dr F. Reigel, Director, Division of Biologicals, Swiss Federal Office of Public Health, Berne, Switzerland

Dr H. Roberts, University of North Carolina Medical School, Chapel Hill, NC, USA (*Temporary Adviser*)

Dr G. Schild, Director, National Institute for Biological Standards and Control, WHO International Laboratory for Biological Standards, Potters Bar, Herts., England (*Temporary Adviser*)

Dr W.G. van Aken, Medical Director, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, WHO International Laboratory for Biological Standards, Amsterdam, Netherlands (*Temporary Adviser*)

Dr D. Wood, National Institute for Biological Standards and Control, WHO International Laboratory for Biological Standards, Potters Bar, Herts., England (*Rapporteur*)

Introduction

The WHO Expert Committee on Biological Standardization met in Geneva from 19 to 23 October 1998. The meeting was opened on behalf of the Director-General by Dr M. Scholtz, Executive Director, Health Technology and Pharmaceuticals.

Dr Scholtz welcomed the members of the Committee, Temporary Advisers and representatives from nongovernmental organizations and industry. He emphasized the importance of the work of the Committee for both developed and developing countries. Biological medicines make an enormous contribution to public health. However, the very nature of biological products raises particular questions regarding their quality control, and he stressed that the considerable potential hazards associated with some of these substances required continuous vigilance.

Dr Scholtz recalled that in May 1997 the World Health Assembly unanimously adopted a resolution on the quality of biological products moving in international commerce (WHA50.20). The resolution recognized the special technical expertise needed for evaluating and controlling biological products, as well as the long-standing and valuable role of WHO's Biologicals unit and the Expert Committee on Biological Standardization. However, the resolution also recognized that WHO's biological standardization activities needed to be strengthened to meet the challenges of the rapid expansion and increasing complexities of the biologicals field.

In pursuance of the resolution, an independent review of WHO's activities in biological standardization was commissioned with a view to recommending action that would enable WHO to respond to scientific developments in a timely manner and to strengthen the mechanisms for providing clear norms and active leadership in promoting the quality, safety and efficacy of biological and biotechnological products. This review was now complete and a draft report of the external review team, which had consulted widely with experts inside and outside WHO, was to be discussed during the meeting.

Dr Scholtz concluded by thanking scientists who participate in WHO meetings, such as those of the Expert Committee on Biological Standardization, and in collaborative studies organized by WHO International Laboratories for Biological Standards and WHO Collaborating Centres, and those members of the Expert Panels on Biological Standardization and on Human Blood Products and Related Substances who comment on proposed standards and requirements. Dr Scholtz also thanked the various nongovernmental organizations that provide support in many ways, as well as the donors of candidate reference

materials, which are, in most cases, the manufacturers of biological materials. All had contributed much to the success of WHO's international biological standardization activities.

General

Developments in biological standardization

The Committee was informed that the change of custodianship of many international reference materials, which had been made necessary by changes in the functioning of two former custodian laboratories, had now been completed. The transfer of international reference materials from the Statens Seruminstitut, Copenhagen, and the Central Veterinary Laboratory, Weybridge, England, to the National Institute for Biological Standards and Control, Potters Bar, England, had been accomplished in a safe and timely manner. This consolidation of the stocks of international reference materials had provided an opportunity to review the continued need for certain preparations and to prioritize needed replacements.

The Committee warmly welcomed the establishment of a new WHO Collaborating Centre for Biological Standardization at the Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD, USA. This significant development was further enhanced by a recent bilateral agreement between the Center for Biologics Evaluation and Research and the National Institute for Biological Standards and Control, to collaborate on regulatory research. The Committee strongly endorsed the development of coordinated international collaborative research initiatives in regulatory areas that concern the safety and efficacy of biological medicines of global public health importance.

The Committee commended the Secretariat for its resourcefulness in obtaining external financial support for many activities in the area of biological standardization. In addition to support provided by the WHO International Laboratories and Collaborating Centres, the Children's Vaccine Initiative had provided support for harmonization activities, the International Society on Thrombosis and Haemostasis had contributed much to the work on standards for haematological products, and the International Association of Biological Standardization had organized specialist meetings to discuss scientific issues relevant to biological standards and the control of biological products during the previous year. The Committee expressed its thanks to these organizations for their