This report presents the recommendations of a WHO Expert Committee commissioned to coordinate activities leading to the adoption of international recommendations for the production and control of vaccines and other biological products used in medicine, and the establishment of international biological reference materials.

Following a brief introduction, the report summarizes a number of issues brought to the attention of the Committee at its meeting held virtually in October 2022. Of particular relevance to manufacturers and national regulatory authorities are the discussions held on the development and adoption of new and revised WHO Recommendations, Guidelines and guidance documents. Following these discussions, the following two documents were adopted on the recommendation of the Committee: (a) Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated); and (b) WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices.

Subsequent sections of the report provide information on the current status, proposed development and establishment of international reference materials in the areas of: biotherapeutics other than blood products; blood products and related substances; cell, tissue and gene therapy products; in vitro diagnostics; standards for use in public health emergencies; and vaccines and related substances.

A series of annexes is then presented which includes an updated list of all WHO Recommendations, Guidelines and other documents related to the manufacture, quality control and evaluation of biological products (Annex 1). The above two WHO documents adopted on the advice of the Committee are then presented as part of this report (Annexes 2 and 3). Finally, all new and replacement WHO international reference standards for biological products established during the October 2022 meeting are summarized in Annex 4. The updated full online catalogue of WHO international reference standards is available at: https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/catalogue.
The World Health Organization was established in 1948 as a specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective and reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications.

The Organization seeks through its publications to support national health strategies and address the most pressing public health concerns of populations around the world. To respond to the needs of Member States at all levels of development, WHO publishes practical manuals, handbooks and training material for specific categories of health workers; internationally applicable guidelines and standards; reviews and analyses of health policies, programmes and research; and state-of-the-art consensus reports that offer technical advice and recommendations for decision-makers. These books are closely tied to the Organization's priority activities, encompassing disease prevention and control, the development of equitable health systems based on primary health care, and health promotion for individuals and communities. Progress towards better health for all also demands the global dissemination and exchange of information that draws on the knowledge and experience of all WHO's Member countries and the collaboration of world leaders in public health and the biomedical sciences.

To ensure the widest possible availability of authoritative information and guidance on health matters, WHO secures the broad international distribution of its publications and encourages their translation and adaptation. By helping to promote and protect health and prevent and control disease throughout the world, WHO's books contribute to achieving the Organization's principal objective – the attainment by all people of the highest possible level of health.

The WHO Technical Report Series makes available the findings of various international groups of experts that provide WHO with the latest scientific and technical advice on a broad range of medical and public health subjects. Members of such expert groups serve without remuneration in their personal capacities rather than as representatives of governments or other bodies; their views do not necessarily reflect the decisions or the stated policy of WHO.

To purchase WHO publications, please contact: WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; email: bookorders@who.int; order online: www.who.int/bookorders.

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

WHO Expert Committee on Biological Standardization
Seventy-fifth report.
WHO Technical Report Series, 1043, 2022 (xii + 252 pages)

WHO Expert Committee on Biological Standardization
Seventy-fourth report.

WHO Expert Committee on Biological Standardization
WHO Technical Report Series, No. 1030, 2021 (xvii + 269 pages)

WHO Expert Committee on Biological Standardization
Seventy-first report.
WHO Technical Report Series, 1028, 2021 (xii + 102 pages)

WHO Expert Committee on Biological Standardization
Sixty-ninth report.
WHO Technical Report Series, No. 1016, 2019 (xviii + 591 pages)

WHO Expert Committee on Biological Standardization
Sixty-eighth report.
WHO Technical Report Series, No. 1011, 2018 (xvi + 380 pages)

WHO Expert Committee on Biological Standardization
Seventieth report.
WHO Technical Report Series, No. 1024, 2020 (xvi + 227 pages)

WHO Expert Committee on Biological Standardization
Sixty-ninth report.
WHO Technical Report Series, No. 1016, 2019 (xv + 251 pages)

WHO Expert Committee on Biological Standardization
Sixty-eighth report.
WHO Technical Report Series, No. 1011, 2018 (xvi + 380 pages)

WHO Expert Committee on Biological Standardization
Sixty-seventh report.

WHO Expert Committee on Biological Standardization
Sixty-sixth report.
WHO Technical Report Series, No. 999, 2016 (xix + 267 pages)

Website: https://www.who.int/health-topics/Biologicals#tab=tab_1
WHO Expert Committee on Biological Standardization

Seventy-sixth 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.
Contents

Abbreviations xiii

1. Introduction 1

2. General 4
   2.1 Strategic directions in biological standardization 4
      2.1.1 Vaccines, biotherapeutics, and cell and gene therapy products: recent and planned activities in biological standardization 4
      2.1.2 Blood products and in vitro diagnostics: recent and planned activities in biological standardization 6
      2.1.3 WHO International Units for serological assays: way forward 8
   2.2 Feedback from custodian laboratories 9
      2.2.1 Scientific issues identified by custodians of WHO international reference standards 9
   2.3 Cross-cutting activities of other WHO committees and groups 13
      2.3.1 Feedback from the 56th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations 13
      2.3.2 Update from the WHO Product Development for Vaccines Advisory Committee 14
      2.3.3 WHO prequalification and WHO emergency use listing 15
      2.3.4 WHO International Nonproprietary Name Expert Group 16
      2.3.5 WHO Model Lists of Essential Medicines 17
      2.3.6 Risk–benefit assessment of antivenoms 19

3. International Recommendations, Guidelines and other matters related to the manufacture, quality control and evaluation of biological products 20
   3.1 Cell, tissue and gene therapy products 20
      3.1.1 Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products 20
   3.2 In vitro diagnostics 21
      3.2.1 WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices 21
   3.3 Vaccines and related substances 23
      3.3.1 Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated) 23

4. International reference materials – biotherapeutics other than blood products 25
   4.1 WHO international reference standards for biotherapeutics other than blood products 25
      4.1.1 First WHO International Standard for cetuximab 25
      4.1.2 First WHO International Reference Panel for antibodies to infliximab 26
      4.1.3 Second WHO International Standard for interleukin-6 (human, recombinant) 28
4.2 Proposed new projects and updates – biotherapeutics other than blood products

4.2.1 Proposed Second WHO International Standard for serum amyloid A

4.2.2 Proposed First WHO International Reference Panel for the characterization of crystallizable fragment domain interactions

5. International reference materials – blood products and related substances

5.1 WHO international reference standards for blood products and related substances

5.1.1 Second WHO International Standard for blood coagulation factor XIII (plasma)


6.1 WHO international reference standards for cell, tissue and gene therapy products

6.1.1 WHO international reference reagents for the quantitation of lentiviral vector copy number – amendment

6.2 Proposed new projects and updates – cell, tissue and gene therapy products

6.2.1 Proposed WHO international reference reagents for flow cytometry analysis of mesenchymal stromal cells and pluripotent stem cells


7.1 WHO international reference standards for in vitro diagnostics

7.1.1 First WHO International Standard for antibodies to chikungunya virus

7.2 Proposed new projects and updates – in vitro diagnostics

7.2.1 Proposed First WHO International Standard for HIV-1 p24 antigen

7.2.2 Proposed Third WHO International Standard for protein S (plasma)


8.1 WHO international reference standards for use in public health emergencies

8.1.1 First WHO International Standard for SARS-CoV-2 antigen

8.1.2 Second WHO International Standard for anti-SARS-CoV-2 immunoglobulin; First WHO International Standard for antibodies to SARS-CoV-2 variants of concern; and First WHO International Reference Panel for antibodies to SARS-CoV-2 variants of concern

8.2 Proposed new projects and updates – standards for use in public health emergencies

8.2.1 Proposed Second WHO International Standard for SARS-CoV-2 RNA for NAT-based assays


9.1 WHO international reference standards for vaccines and related substances

9.1.1 First WHO international standards for anti-human papillomavirus types 6, 11, 31, 33, 45, 52 and 58 serum

9.1.2 WHO International Reference Reagent for tetanus antitoxin for use in flocculation test (equine)

9.1.3 Third WHO International Standard for antibodies to rabies virus

9.1.4 WHO international reference reagents for potency testing of inactivated poliomyelitis vaccines
9.2 Proposed new projects and updates – vaccines and related substances

9.2.1 Proposed Second WHO International Standard for yellow fever vaccine

9.2.2 Update on the WHO collaborative study to investigate the utility of next generation sequencing of virus stocks used in the manufacture of oral poliomyelitis vaccines

<table>
<thead>
<tr>
<th>Annex 1</th>
<th>WHO Recommendations, Guidelines and other documents related to the manufacture, quality control and evaluation of biological products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Annex 2</th>
<th>Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Annex 3</th>
<th>WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WHO Medical device technical series</td>
</tr>
<tr>
<td></td>
<td>179</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Annex 4</th>
<th>New and replacement WHO international reference standards for biological products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>327</td>
</tr>
</tbody>
</table>
WHO Expert Committee on Biological Standardization
Seventy-sixth meeting held virtually 24 to 28 October 2022

Committee members¹
Dr K.M. Boukef, University of Monastir, Monastir, Tunisia
Dr C. Burns, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Professor K. Cichutek, Paul-Ehrlich-Institut, Langen, Germany (Vice-chair)
Dr M. Darko,² Food and Drugs Authority, Accra, Ghana
Dr A.E. del Pozo,² Hospital de Pediatria Garrahan, Buenos Aires, Argentina
Dr I. Feavers, Consultant, Nacton, the United Kingdom (Rapporteur)
Professor I. Fradi-Dridi, Direction de la Pharmacie et du Médicament, Tunis, Tunisia
Professor S. Hindawi, King Abdulaziz University, Jeddah, Saudi Arabia (Vice-chair)
Mrs T. Jivapaisarnpong, Advisor, King Mongkut’s University of Technology Thonburi, Bangkok, Thailand
Professor G. Kang, Christian Medical College, Vellore, India
Professor M.B.C. Koh, St George’s Hospital Medical School, London, the United Kingdom; and Health Sciences Authority, Singapore, Singapore (Co-rapporteur)
Dr R. May, Dubai Health Authority, Dubai, United Arab Emirates
Ms C. Morris, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Professor D.H. Muljono, Hasanuddin University, Makassar, Indonesia
Dr K. Quillen, Atrius Health, Boston, MA, the United States of America (USA)
Dr Y. Sohn, Seoul National University, Seoul, Republic of Korea
Dr J. Southern, Representative of the South African Health Products Regulatory Authority, Simon’s Town, South Africa
Dr P. Strengers, Consultant, Amsterdam, Netherlands
Dr J. Wang, National Institutes for Food and Drug Control, Beijing, China
Dr Y. Wang, National Institutes for Food and Drug Control, Beijing, China

¹ The decisions of the Committee were taken in closed session with only members of the Committee and WHO Secretariat 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.

² Unable to attend.
Dr S. Wendel, Hospital Sirio-Libanês, São Paulo, Brazil
Dr C. Witten, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, the USA (Chair)

Temporary advisors
Dr C.A. Bravery, Consultant, London, the United Kingdom
Dr M. Buda, European Directorate for the Quality of Medicines & Healthcare, Strasbourg, France
Dr K. Chumakov, Center for Biologics Evaluation and Research, US Food and Drug Administration, Bethesda, MD, the USA
Dr A. Geyer, Agência Nacional de Vigilância Sanitária, Sao Paulo, Brazil
Dr E. Griffiths, Consultant, Kingston upon Thames, the United Kingdom
Mrs J. Hansen, Consultant, Netherlands
Dr C. Li, National Institutes for Food and Drug Control, Beijing, China
Dr N.G. Mahlangu, Consultant, Harare, Zimbabwe
Dr L. Mallet, European Directorate for the Quality of Medicines & Healthcare, Strasbourg, France
Dr J. Martin, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr B.D. Mosweu, Botswana Medicines Regulatory Authority, Gaborone, Botswana
Dr P. Salmikangas, Consultant, Klauskala, Finland
Dr D. Teo, Visiting Consultant, Blood Services Group, Health Sciences Authority, Singapore, Singapore
Dr A.L. Waddell, Stanley, the United Kingdom (Editor of the report of the Committee)
Dr M. Wierer, European Directorate for the Quality of Medicines & Healthcare, Strasbourg, France
Dr T. Wu, Biologic and Radiopharmaceutical Drugs Directorate, Health Canada, Ottawa, Canada

State actors
Dr N. Almond, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr R. Asally, Saudi Food and Drug Authority, Riyadh, Saudi Arabia
Dr M. Bailey, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
WHO Expert Committee on Biological Standardization
Seventy-sixth report

Dr E. Bentley, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr P. Bowyer, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr K. Cornish, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr B. Cowper, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr J. Fryer, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr I. Hamaguchi, National Institute of Infectious Diseases, Tokyo, Japan
Dr M. Hassall, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr A. Hilger, Paul-Ehrlich-Institut, Langen, Germany
Dr J. Hogwood, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr K. Ishii, National Institute of Infectious Diseases, Tokyo, Japan
Dr A. Ishii-Watabe, National Institute of Health Sciences, Kawasaki, Japan
G. Jotwani, Indian Council of Medical Research, New Delhi, India
Dr S. Kempster, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr M. Majumdar, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr P. Marks, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, the USA
Dr Y. Maruyama, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan
Dr G. Mattiuzzo, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
F.C. Melo, Agência Nacional de Vigilância Sanitária, Brasília, Brazil
Dr H. Meyer, Paul-Ehrlich-Institut, Langen, Germany
Dr P. Minor, Consultant, St Albans, the United Kingdom
Dr M. Nübling, Paul-Ehrlich-Institut, Langen, Germany

3 Unable to attend.
Dr M. Ochiai, National Institute of Infectious Diseases, Tokyo, Japan
I.U. Oh, Ministry of Food and Drug Safety, Chungscheongbuk-do, Republic of Korea
Dr M. Page, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr R.M. Parca, Agência Nacional de Vigilância Sanitária, Brasília, Brazil
Dr G. Prescott, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr S. Prior, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr S. Rajagopal, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr G. Raychaudhuri, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, the USA
Dr I.G. Reischl, Austrian Medicines and Medical Devices Agency, Vienna, Austria
Dr A. Riches, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr P. Rigsby, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr N. Rose, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr M. Rosu-Myles, Biologic and Radiopharmaceutical Drugs Directorate, Health Canada, Ottawa, Canada
Dr S-R. Ryu, Ministry of Food and Drug Safety, Chungscheongbuk-do, Republic of Korea
Dr Y. Sato, National Institute of Health Sciences, Kawasaki, Japan
Dr C. Schärer, Swiss Agency for Therapeutic Products, Bern, Switzerland
Dr I. Shin, Ministry of Food and Drug Safety, Chungscheongbuk-do, Republic of Korea
Dr S.C. da Silveira Andreoli, Agência Nacional de Vigilância Sanitária, Brasília, Brazil
Dr L. Stephens, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr P. Stickings, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr Y. Takahashi, National Institute of Infectious Diseases, Tokyo, Japan
Dr I. Takao, National Institute of Health Sciences, Kawasaki, Japan
Dr A. Tedcastle, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom
Dr C. Thelwell, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom

Dr G. Unger, Paul-Ehrlich-Institut, Langen, Germany

Dr W. Urassa, Consultant, Dar es Salaam, United Republic of Tanzania

Dr A. Vasheghani, Food and Drug Organization, Tehran, the Islamic Republic of Iran

Dr N. Verdun, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, the USA

Dr M. Wadhwa, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom

Dr J. Weir, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, the USA

Dr D. Wilkinson, Medicines and Healthcare products Regulatory Agency, Potters Bar, the United Kingdom

Dr M. Xu, National Institutes for Food and Drug Control, Beijing, China

Observers from non-state actors in official relations

*International Alliance for Biological Standardization*

Dr R. Sheets

*International Generic and Biosimilar Medicines Association*

Dr J. Marechal, Brussels, Belgium

*International Federation of Pharmaceutical Manufacturers & Associations*

Dr M. Gencoglu

*International Society on Thrombosis and Haemostasis*

Dr J. Meijers, Amsterdam, Netherlands

*United States Pharmacopeia Convention*

Dr F. Atouf, Rockville, MD, the USA

Dr D. McCarthy, Rockville, MD, the USA

Representation from intergovernmental and other entities

*Africa Society for Blood Transfusion*

Dr M. Farouk, Cairo, Egypt

*Biotechnology Innovation Organization*

Dr L. Harden

*Coalition for Epidemic Preparedness Innovations*

Dr V. Bernasconi, Oslo, Norway
Developing Countries Vaccine Manufacturers Network
Dr R.C. Guimarães

European Medicines Agency
Ms D. Rogers

Plasma Protein Therapeutics Association
Dr D. Misztela, Brussels, Belgium

World Health Organization (WHO)
Access to Medicines and Health Products (MHP)
Dr M. Simão, Assistant Director-General

Health Products Policy and Standards (MHP/HPS)
Dr C. Ondari, Director

Technical Standards and Specifications (MHP/HPS/TSS)
Dr I. Knezevic (Secretary to the Committee; Lead for the vaccines and biotherapeutics track)
Dr Y. Maryuningsih (Lead for the blood products and in vitro diagnostics track)
Ms S. Jenner
Dr R. Isbrucker
Dr H-N. Kang
Dr D. Lei
Dr J. Yu
Dr T. Zhou

INN and Classification of Medical Products (MHP/HPS/INN)
Dr R. Balocco

Norms and Standards for Pharmaceuticals (MHP/HPS/NSP)
Dr H. Schmidt

Essential Medicines (MHP/HPS/MIA/EML)
Dr L. Moja

Vaccines and Immunization Devices Assessment (MHP/RPQ/PQT/VAX)
Dr C. Rodriguez-Hernandez

Regulation and Safety (MHP/RPQ/REG)
Dr A. Kijo

Product and Delivery Research (UHL/IVB/PDR)
Dr B. Giersing
Representation from WHO regional offices

WHO Regional Office for the Americas
Dr A. Lemgruber
Dr M.L. Pombo

WHO Regional Office for the Western Pacific
Dr J. Shin

Unable to attend: WHO Regional Office for Africa; WHO Regional Office for South-East Asia; WHO Regional Office for Europe; and WHO Regional Office for the Eastern Mediterranean.
**Abbreviations**

AG-BRAS  Advisory Group for Blood Regulation, Availability and Safety  
ADA  anti-drug antibody  
ADCC  antibody-dependent cellular cytotoxicity  
BAU  binding antibody unit(s)  
BCG  bacillus Calmette–Guérin  
CBER  Center for Biologics Evaluation and Research  
CHIKV  chikungunya virus  
CHIM  controlled human infection model(s)  
CI  confidence interval  
cIPV  conventional inactivated poliomyelitis vaccine  
COVID-19  coronavirus disease 2019  
cVDPV  circulating vaccine-derived poliovirus  
ddPCR  droplet digital polymerase chain reaction  
DNA  deoxyribonucleic acid  
ECSPP  Expert Committee on Specifications for Pharmaceutical Preparations  
EDQM  European Directorate for the Quality of Medicines & HealthCare  
EGFR  epidermal growth factor receptor  
ELISA  enzyme-linked immunosorbent assay  
EML  WHO Essential Medicines List  
EUL  WHO emergency use listing  
Fab  antigen binding fragment (domain)  
FAVN  fluorescent antibody virus neutralization (test)  
Fc  crystallizable fragment (domain)  
FXIII  blood coagulation factor XIII  
GBT  WHO global benchmarking tool  
GBT + Blood  WHO global benchmarking tool plus blood  
GCV  geometric coefficient of variation
GMP  good manufacturing practice(s)
GMRF  WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices
GPEI  Global Polio Eradication Initiative
HIV  human immunodeficiency virus
HPV  human papillomavirus
HRIG  human rabies immunoglobulin
HTS  high-throughput sequencing
ICDRA  International Conference of Drug Regulatory Authorities
ICSPP  International Coalition for Safe Plasma Protein Products
IFU  instructions for use
IL-6  Interleukin-6
INN  international nonproprietary name(s)
IOP  inhibition of proliferation (assay)
IPV  inactivated poliomyelitis vaccine
ISA  international standard(s) for antibiotics
ISBT  International Society of Blood Transfusion
ISCT  International Society for Cellular Therapy
ISTH  International Society of Thrombosis and Haemostasis
IU  International Unit(s)
IVD  in vitro diagnostic
Lf  limit of flocculation
LMIC  low- and middle-income countries
LV  lentiviral
mAb  monoclonal antibody
MAPREC  mutant analysis by polymerase chain reaction and restriction enzyme cleavage
MHRA  Medicines and Healthcare products Regulatory Agency
mRNA  messenger RNA
MSC  mesenchymal stromal cell
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAT</td>
<td>nucleic acid amplification technique</td>
</tr>
<tr>
<td>NC3Rs</td>
<td>National Centre for the Replacement, Refinement &amp; Reduction of Animals in Research</td>
</tr>
<tr>
<td>nOPV</td>
<td>novel oral poliomyelitis vaccine</td>
</tr>
<tr>
<td>NRA</td>
<td>national regulatory authority</td>
</tr>
<tr>
<td>OPV</td>
<td>oral poliomyelitis vaccine</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PDMP</td>
<td>plasma-derived medicinal product</td>
</tr>
<tr>
<td>PDVAC</td>
<td>WHO Product Development for Vaccines Advisory Committee</td>
</tr>
<tr>
<td>PEI</td>
<td>Paul-Ehrlich-Institut</td>
</tr>
<tr>
<td>Ph. Eur.</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>PQ</td>
<td>WHO prequalification</td>
</tr>
<tr>
<td>PSC</td>
<td>pluripotent stem cell</td>
</tr>
<tr>
<td>PVNA</td>
<td>pseudovirus neutralization assay</td>
</tr>
<tr>
<td>qPCR</td>
<td>quantitative polymerase chain reaction</td>
</tr>
<tr>
<td>RDT</td>
<td>rapid diagnostic test</td>
</tr>
<tr>
<td>RFFIT</td>
<td>rapid fluorescent focus inhibition test</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>rp24</td>
<td>recombinant p24</td>
</tr>
<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts on Immunization</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>severe acute respiratory syndrome coronavirus 2</td>
</tr>
<tr>
<td>sIPV</td>
<td>Sabin inactivated poliomyelitis vaccine</td>
</tr>
<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
</tr>
<tr>
<td>TPP</td>
<td>target product profile</td>
</tr>
<tr>
<td>VLP</td>
<td>virus-like particle</td>
</tr>
<tr>
<td>VOC</td>
<td>variant(s) of concern</td>
</tr>
<tr>
<td>WHOCC</td>
<td>WHO collaborating centre</td>
</tr>
<tr>
<td>WPV</td>
<td>wild poliovirus</td>
</tr>
</tbody>
</table>
1. Introduction

The seventy-sixth meeting of the WHO Expert Committee on Biological Standardization was held virtually from 24 to 28 October 2022. The meeting was opened on behalf of the Director-General of WHO and the Assistant Director-General, Access to Medicines and Health Products, by Dr Clive Ondari, Director, Health Products Policy and Standards. Dr Ondari began by welcoming the Committee members, meeting participants and observers. He noted that the now 22-member Committee was well balanced with regard to its expertise, and gender and geographical representativeness. Dr Ondari went on to inform meeting participants of the untimely death of Committee member Dr Patricia Aprea, Director of Evaluation and Control of Biologicals and Radiopharmaceuticals at the National Administration of Drugs, Food and Medical Devices in Argentina. Highlighting Dr Aprea’s expert contributions, including as a drafting group member for the recently published WHO Guidelines on evaluation of biosimilars, Dr Ondari observed that her passing represented a significant loss to the Committee.

Dr Ondari informed meeting participants that the Seventy-fifth World Health Assembly had been the first to be held in person since the start of the coronavirus disease 2019 (COVID-19) pandemic. A key theme had been strengthening preparedness and response activities for health emergencies, and in this context the Health Assembly had recognized the contribution made by this Committee. Acknowledgement had also been made of the role of the Committee in polio eradication efforts – another vitally important area for WHO and its partners. Since 2020, the work of WHO had been broadly divided into COVID-19 and non-COVID-19 activities and the broad range of topics to be discussed at the current meeting would once again span both categories. Dr Ondari expressed his appreciation for the work of all the WHO collaborating centres (WHOCCs), highlighting in particular the role of the Medicines and Healthcare products Regulatory Agency (MHRA) as the custodian laboratory for the majority of WHO measurement standards. Reflecting on the need to establish such measurement standards in a timely manner, Dr Ondari noted that the Committee now met twice a year.

With regard to WHO written standards, Dr Ondari highlighted the two documents to be considered for adoption at the current meeting – namely the WHO Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated) and the WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices. Documents now nearing finalization included the WHO Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related products intended for the prevention or treatment of infectious diseases – of particular importance in the development of COVID-19 therapeutic products.
– and a WHO considerations document on the development of a regulatory framework for human cells and tissues and for advanced therapy medicinal products. Dr Ondari continued by underlining the achievements of the Advisory Group for Blood Regulation, Availability and Safety (AG-BRAS) since its inception, and welcomed the revival of the Achilles project which aims to improve blood safety and reduce plasma wastage worldwide. Dr Ondari concluded by thanking the Committee members, WHO Secretariat, other WHO colleagues and all meeting participants for their invaluable contributions.

Dr Ivana Knezevic, Secretary to the Committee, thanked Dr Ondari for his opening remarks. Dr Knezevic reminded meeting participants that WHO operates at headquarters, regional office and country office levels, and as the specialized United Nations agency responsible for providing leadership on global health matters and shaping the health research agenda, the setting of norms and standards, and promoting their implementation, remain core WHO functions. Dr Knezevic went on to remind meeting participants of two important resolutions adopted by the Sixty-seventh World Health Assembly in 2014 that were of particular relevance to the work of the Committee – namely, resolution WHA67.21 on access to biotherapeutic products including biosimilars, and resolution WHA67.20 on regulatory strengthening. Dr Knezevic reminded participants that the reports of all WHO expert committees were presented to the WHO Executive Board, which had recently encouraged the further expansion of the WHO Expert Advisory Panel from which expert committee members were drawn to ensure their geographical and gender representativeness.

Dr Knezevic then introduced each of the Committee members and outlined the procedures and working arrangements of the meeting. An open information-sharing session involving all participants including non-state actors would be held on Monday 24 October 2022. Committee members, regulatory authority representatives and subject matter experts from governmental organizations would then participate in the main meeting from Monday 24 October to Thursday 27 October 2022. The final decisions and recommendations on the adoption of WHO written standards and the establishment of WHO measurement standards would then be made in a closed session held on Friday 28 October attended only by Committee members and the WHO Secretariat. Dr Knezevic concluded by thanking Committee members, WHO colleagues, members of drafting and working groups, WHOCC and custodian laboratory representatives and staff, and the many individual experts present for their continued efforts.

Following the conclusion of the open information-sharing session, the meeting officials were elected. In the absence of dissent, Dr Celia Witten was elected as Chair with Professor Klaus Cichutek and Dr Salwa Hindawi as Vice-chairs. Dr Ian Feavers and Professor Mickey Koh were elected as Rapporteur and Co-rapporteur respectively. Dr Knezevic presented the declarations of interests
completed by all members of the Committee, and by WHO temporary advisers and other participants. After evaluation, WHO had concluded that none of the interests declared constituted a significant conflict of interest and that the individuals concerned would be allowed to participate fully in the meeting.

The Committee then adopted the proposed agenda and timetable (WHO/BS/2022.2440).
2. General

2.1 Strategic directions in biological standardization

2.1.1 Vaccines, biotherapeutics, and cell and gene therapy products: recent and planned activities in biological standardization

Dr Knezevic began by acknowledging the crucial role of WHOCCs in the development both of WHO measurement standards and of WHO written standards, and in facilitating their subsequent implementation workshops. WHO was currently collecting annual reports from all WHOCCs despite the difficulties caused by the COVID-19 pandemic. WHOCCs were designated for 4 years, with Dr Knezevic noting that the re-designation of the WHOCC within the Ministry of Food and Drug Safety in the Republic of Korea was expected to be completed in early 2023. Dr Knezevic also noted that the next meeting of the WHO network of collaborating centres on standardization and regulatory evaluation of vaccines would be held in 2023, and she was pleased to announce that WHO would also now revert to holding face-to-face implementation workshops. Dr Knezevic further noted that the full report of the April 2022 meeting of the Committee had now been published.5

Dr Knezevic went on to provide an overview of WHO written standards for biologicals that had either been recently adopted or were undergoing development or revision. Along with its Recommendations and Guidelines, WHO also publishes other high-level written standards for regulators and manufacturers of biological products. Recently published WHO written standards applicable to COVID-19 vaccines, therapeutics and diagnostics had included the WHO Guidelines on the quality, safety and efficacy of plasmid DNA vaccines, and a WHO regulatory considerations document on evaluating the quality, safety and efficacy of messenger RNA (mRNA) vaccines for the prevention of infectious diseases. In addition, revised WHO Guidelines for the production and quality control of monoclonal antibodies and related products intended for medicinal use had been adopted on the recommendation of the Committee in April 2022. Companion WHO Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related products intended for the prevention or treatment of infectious diseases were currently being subjected to public consultation and would be presented to the Committee for consideration at its next meeting in March 2023. The WHO manual for the preparation of reference materials for use as secondary standards in antibody testing, with its focus on

---

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody testing, had also been adopted at the previous meeting and case studies for the first implementation workshop were now being prepared.

Dr Knezevic then presented a summary overview of a range of non-COVID-19-related WHO written standards for vaccines that the Committee had previously recommended for updating in light of recent scientific and technological advances. These included the revised WHO Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated) scheduled for submission at the current meeting (see section 3.3.1 below), along with other WHO written standards on yellow fever vaccines, rotavirus vaccines, and measles, mumps and rubella (and combined) vaccines. In addition, a review of tuberculosis vaccine developments would be conducted in 2023 with a view to revising WHO written guidance on bacillus Calmette–Guérin (BCG) vaccines, with malaria vaccines and dengue vaccines guidance also scheduled for review. Depending on the outcomes of ongoing vaccine developments in the respective fields, new WHO written standards may also be required for enteric vaccines and Group B streptococcal vaccines.

In addition to documents on specific vaccines, a number of more general vaccine-related WHO written standards now required revision. These include the WHO Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries, and WHO Guidelines on procedures and data requirements for changes to approved vaccines. The WHO Guidelines for independent lot release of vaccines by regulatory authorities would also be reviewed to identify required changes. The WHO Recommendations for the preparation, characterization and establishment of international and other biological reference standards was also currently under review with a view to developing two separate documents – one to provide guidance to custodian laboratories and the other for end-users of such standards.

To support other key regulatory systems strengthening efforts, the WHO global model regulatory framework for medical devices including in vitro diagnostic medical devices had now been revised and would be submitted for adoption at the current meeting (see section 3.2.1 below). A guidance document on the development of a regulatory framework for human cells and tissues and for advanced therapy medicinal products would also be discussed during the current meeting (see section 3.1.1 below) and is expected to be submitted to the Committee at its next meeting in March 2023.

Dr Knezevic went on to summarize a number of other recent developments, including the outcomes of a short survey of the current use of high-throughput sequencing (HTS) technologies for the detection of adventitious agents during the evaluation of vaccines and biotherapeutics. Eight national regulatory authorities (NRAs), including seven WHOCCs, provided
information on the current situation, and indicated their expectations regarding the amendment of WHO written standards on cell substrates. Although the responses were diverse, there was a consensus that such amendment was needed to align the guidance with corresponding guidance from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Dr Knezevic reminded meeting participants that a panel of five WHO international reference reagents for adventitious agent detection using HTS technologies had been established in October 2020, with further viruses to be added to the panel.

Dr Knezevic then reminded meeting participants of the adoption in April 2022 of the revised WHO Guidelines on evaluation of biosimilars and noted that a number of background documents explaining the rationale for the revision had now been published. Informal consultations and workshops were now being planned to support implementation of the Guidelines. Dr Knezevic went on to note that a second round of public consultation on the above-mentioned WHO guidance document on the development of a regulatory framework for human cells and tissues and for advanced therapy medicinal products had now concluded and an update on progress would be provided at the current meeting (see section 3.1.1 below). Submission of the document to the Committee was scheduled for March 2023. A survey would be carried out to better understand the current global regulatory landscape in this area and to inform the further development of related WHO written standards, followed by an international workshop to assess the need for associated WHO measurement standards for advanced products. Following an overview of other WHO consultations and implementation workshops, and related conferences organized by external partners, scheduled for 2022–2023, Dr Knezevic concluded by thanking her colleagues at WHO, all members of the WHO written standards drafting groups, WHOCCs and custodian laboratories, and individual experts for their invaluable support and contribution.

2.1.2 Blood products and in vitro diagnostics: recent and planned activities in biological standardization

Dr Yuyun Maryuningsih began by reviewing the activities of AG-BRAS – an advisory group that had been established in 2021 to provide wide-ranging expert guidance on both blood regulation and transfusion medicine. Following its review of WHO blood-related documents, AG-BRAS had reported that 50 of the 94 documents now required updating and that six were obsolete. Currently, 13 such documents were being updated. Other AG-BRAS activities had included the harmonization of definitions and terminology in the blood area, as well as the development of a strategy for the dissemination and promotion of WHO documents. In addition, AG-BRAS had carried out a compliance check between
the published guidance of WHO and the Association for the Advancement of Blood and Biotherapies.

Dr Maryuningsih then provided an update on the ongoing implementation of the WHO Action framework to advance universal access to safe, effective and quality-assured blood products 2020–2023. Consisting of six strategic objectives and supported by 10 associated guidance resources, the Action framework provides strategic direction both to WHO activities and worldwide efforts in this area. Of the 10 guidance resources, five had now been implemented, with the aim of finalizing implementation of the remaining components by the end of 2023. Webinars promoting the Action framework and other WHO resources, along with associated training and technical assistance, would continue to be undertaken at country level. Dr Maryuningsih highlighted the example of the Action framework guidance on increasing the supply of plasma-derived medicinal products (PDMPs) in low- and middle-income countries (LMIC) through the fractionation of domestic plasma. Following publication of a WHO white paper on this subject, WHO held a webinar, conducted in six languages and attended by ministries of health, NRAs, blood establishments and other stakeholders, including patient groups. Participants strongly felt that efforts in this area should continue, including through the establishment of an international platform of key stakeholders under the aegis of WHO and the International Society of Blood Transfusion (ISBT) that would respond to country requests for assistance. During 2022, the WHO Blood and other Products of Human Origin (BTT) team had also supported a number of regulatory strengthening activities by providing training on the WHO global benchmarking tool + blood (GBT + Blood), with plans to also conduct training on good manufacturing practices (GMP) for blood establishments in French-speaking African countries and in the WHO Region of the Americas in 2023.

Given the similarity between the aims of the WHO Action framework and the Achilles project, launched in 2009, WHO had decided to revive the project based on the above WHO white paper on increasing the supply of PDMPs in LMIC, which sets out guidance in a number of key areas. Aware that this project could not be undertaken in isolation, WHO would collaborate with ISBT and with members of the ISBT-hosted International Coalition for Safe Plasma Protein Products (ICSPP) for a five-year period (2022–2027). Activities under the revived Achilles project would include supporting the introduction of new production technologies for safe plasma products in LMIC, facilitating the implementation and sustainability of such production, and empowering LMIC to alleviate existing supply issues. Dr Maryuningsih went on to highlight a related proposal to include pathogen-reduced cryoprecipitate in the WHO Essential Medicines List (EML). Led by BTT and ISBT, a working group lead by BTT and ISBT had been established to draft the proposal.
Dr Maryuningsih concluded by briefly summarizing the WHO measurement standards relevant to this area that were being proposed for consideration by the Committee at the current meeting in light of the outcomes of a May 2022 meeting of the WHO network of collaborating centres for blood products and in vitro diagnostics.

While congratulating WHO on its efforts to ensure the wider availability of safe plasma, and welcoming the associated proposal, the Committee noted the typically limited resources available in LMIC to implement the technologies required. Noting that the above proposal was still at an early stage, Dr Maryuningsih assured the Committee that there had been considerable interest expressed in this initiative both within and outside WHO.

2.1.3  **WHO International Units for serological assays: way forward**

Dr Mark Page reminded the Committee that in December 2020 the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin had been established. Given the diversity of antibody binding assays and their target analytes, a potency value in International Units (IU) had been assigned only for neutralizing antibody activity. However, in order to facilitate comparison of binding antibody assays detecting the same class of immunoglobulin with the same specificity, an arbitrary unitage of 1000 binding antibody units (BAU)/mL had also been assigned to the same material. Although widely accepted in the field, the introduction of BAU was subsequently criticized on the grounds that it introduced a different unit name for the same kind of quantity – as opposed to using different names for the analyte – and thus represented a departure from accepted nomenclature conventions, including the conventions used by WHO when assigning IU. Responding in the scientific press, WHO had reiterated the original concern of the Committee – namely that reporting both biological activity and antibody binding in the same unit risked the inappropriate comparison of neutralizing antibody titres with those of different binding antigens. Furthermore, the WHO international standard had been established explicitly for use only in neutralization assays, with the same material, when used to harmonize antibody binding assays, only having the status of an interim MHRA “research reagent”. Dr Page then provided the Committee with further evidence that the reference material, when used as indicated in the instructions for use (IFU), was indeed highly effective in harmonizing antibody binding assays for specific target antigens of the same immunoglobulin class. However, Dr Page also highlighted a number of previous and potential future problems arising from the misuse of such reference materials, and guidance from the Committee was now being sought on how best to ensure consistency and clarity in the assignment of unitages for use in antibody binding assays.

The Committee noted that four prospective WHO international standards for use in serological assays would be considered for establishment at
the current meeting, with a variety of approaches being proposed for assigning their neutralizing antibody and binding antibody unitages. The Committee considered that unless a reference material supported a therapeutic decision based on a clinical correlation with antibody binding activity there was a case for not assigning IU for this type of activity. In addition, vaccine manufacturers and diagnostic kit developers used a wide variety of serological platforms to measure different analytes and different antibody activities, with resulting potential for confusion when using the same reference material to harmonize all such assays. In addition, the inappropriate use of WHO reference materials to correlate antibody binding titres with functional antibody levels (and hence with protective thresholds) could further add to the confusion.

Recognizing the potential loss of confidence in such WHO international standards, the Committee recommended that a working group be established to set out the fundamental issues in this area and to provide recommendations on how best to proceed in the longer term. Regarding the materials to be reviewed at the current meeting, the Committee would consider each on a case-by-case basis with regard to the assignment of potency values for antibody binding. Accepting that the use of BAU was already well established with respect to SARS-CoV-2 antibody assays, the Committee suggested that consideration be given to revising the text of the IFU for clarity, and recommended that the current practice should continue until the working group had reported its conclusions.

2.2 Feedback from custodian laboratories

2.2.1 Scientific issues identified by custodians of WHO international reference standards

Center for Biologics Evaluation and Research (CBER), Silver Springs, MD, the USA

Dr Celia Witten reviewed the recent vaccine-related activities of CBER, which had included the prospective replacement and expansion of the previously established panel of WHO international reference reagents for adventitious virus detection in biological products using HTS technologies, and the development of universal mAb reagents for the potency testing both of conventional inactivated poliomyelitis vaccines (cIPVs) and of Sabin inactivated poliomyelitis vaccines (sIPVs).

Dr Witten began by noting that the development of COVID-19 vaccines had led to increased demand for the five WHO international reference reagents for use in adventitious virus testing established in 2020. Replacement of the initially limited number of vials was currently under way with the prospective replacement panel now including two additional virus families (coronavirus and parvovirus) to expand its range. The proposed panel would be submitted to the Committee for its consideration in October 2023.
A project endorsed by the Committee in 2018 to develop universal reagents for IPV potency testing based on human and mouse mAbs had now been completed. The outcomes of the international collaborative study and associated proposals would be presented for consideration by the Committee at the current meeting (see section 9.1.4 below). In addition, CBER, together with MHRA, had led a collaborative study to support the replacement of animal neurovirulence testing with HTS-based technologies for the routine lot release of oral poliomyelitis vaccine (OPV) and consistency monitoring of sIPV production. A report and associated proposal on this would also be presented to the Committee at the current meeting (see section 9.2.2 below).

CBER had also been involved in the drafting of several recent WHO written standards and other documents, including: (a) the revised WHO Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated) (see section 3.3.1 below); (b) the revised WHO Guidelines to assure the quality, safety and efficacy of live attenuated rotavirus vaccines; (c) the report of the National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs) project to review WHO written standards and make recommendations concerning their animal testing requirements and procedures; and (d) the WHO guidance document on the development of a regulatory framework for human cells and tissues and for advanced therapy medicinal products (see section 3.1.1 below). Dr Witten then provided a summary of recent CBER collaboration in the development of WHO measurement standards, several of which would be presented to the Committee at the current meeting.

Looking ahead, Dr Witten highlighted that CBER was considering developing an adenovirus reference material due to the increased use of adenoviral vectors in cancer therapies and vaccine development, including COVID-19 vaccine development. Although an adenovirus type 5 reference material had been available for 20 years, stocks were now depleted and a replacement material was needed. Dr Witten concluded by informing the meeting that following the recent establishment of the Eighth WHO International Standard for blood coagulation factor VIII concentrate, stocks of the historical standards were now obsolete and any request to retain these materials for future collaborative studies should be made prior to their scheduled destruction in 2023.

After being informed that MHRA also intended to develop adenovirus reference materials, and recognizing the importance of face-to-face meetings in addressing topics of mutual interest, the Committee suggested that MHRA and CBER consider the potential benefits of collaborating in the development of a panel of different adenovirus serotypes.
Dr Laurent Mallet began by reminding meeting participants that since 2006 EDQM has been the custodian laboratory for international standards for antibiotics (ISA) and currently holds and distributes 23 ISA without cost recovery. The demand for such standards remains steady at 10–20 vials of each ISA per year, and there were no new issues to report. At the current level of demand, none of the ISAs would need to be replaced in the next 2 years. Dr Mallet went on to note the decision made in 2020 that MHRA would no longer serve as the custodian laboratory for equine serum gonadotrophin reference materials and would not replace the Second WHO International Standard for serum gonadotrophin (equine). The Committee had requested that EDQM consider taking on the role of custodian laboratory and leading a collaborative study to develop a replacement reference material. Dr Mallet reported that having evaluated its feasibility, EDQM was not in a position to undertake such a study and suggested that another custodian laboratory be sought.

Dr Mallet then provided an update on the work being conducted at EDQM to replace two in vivo tests – which had direct implications for the application of the 3Rs principles (Replacement, Refinement, Reduction) regarding the use of animals in research. The first of these projects involved an international collaborative study to validate a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) as an in vitro alternative to the current in vivo potency test for rabies vaccines. A set of samples consisting of 11 vaccines and five virus strains, along with a standard operating procedure and reagents, had been distributed to 31 participants worldwide to evaluate the transferability and robustness of the method. Preliminary study findings indicated that participants obtained comparable results and that intra- and inter-laboratory variation were both within the ranges expected for ELISA methods. The report of this phase of the project was now being prepared.

A second project to eliminate animal-based pyrogen testing from the European Pharmacopoeia (Ph. Eur.) by 2026 remained on course. Despite changes to relevant texts aimed at encouraging users to perform in vitro tests, the rabbit pyrogen test continued to be widely used. The project would therefore culminate in the removal of the current pyrogenicity chapter of the Ph. Eur. and its replacement with a new chapter based on the use of the bacterial endotoxin test, monocyte activation test or both depending on the outcome of risk analysis.

Reflecting on the large number of animals needed to evaluate the potency of rabies vaccines the Committee welcomed the ongoing development of in vitro alternatives such as ELISA, and agreed that such developments represent a significant improvement in the quality control of vaccines.
Dr Marc Bailey began by welcoming the upcoming WHO guidance document on the development of a regulatory framework for human cells and tissues and for advanced therapy medicinal products, scheduled for discussion at the current meeting (see section 3.1.1 below). Dr Bailey noted that the standardization of such products was still in its infancy and there was therefore a need for a WHO strategy to help WHOCCs define their future programmes in this area, along with a need to add appropriate expertise to the Committee. Dr Bailey noted in particular the importance of stakeholder consensus on the reference standards that would be required for viral vectors, CAR-T cell therapies and stem cell based therapies, and indicated the willingness of MHRA to support a workshop or similar process to engage with this community.

Dr Bailey went on to note that MHRA was currently the custodian of five WHO international standards for therapeutic mAbs – with such standards being in considerable demand worldwide. The programme to develop further such standards was proceeding at pace and Dr Bailey highlighted the proposed standard for cetuximab and a proposal to develop reference reagents for Fc domain interactions, both of which would be considered by the Committee at the current meeting (see sections 4.1.1 and 4.2.2 respectively).

Dr Bailey further noted the similarly high level of global demand for bacterial polysaccharide standards from a range of users, including the manufacturers of conjugate vaccines. Looking ahead, Dr Bailey indicated that the proposed replacement reference material for serogroup C meningococcal polysaccharide due to be considered by the Committee in March 2023 might raise a number of issues due to the use of an alternative method for value assignment, and the possible need for method-specific value assignment. Dr Bailey concluded by summarizing the reference materials that were due to be submitted for consideration by the Committee in March 2023, along with a proposal to develop a reference reagent for lipid-nanoparticle-encapsulated mRNA products.

The Committee specifically noted the increasing importance of international reference standards for therapeutic mAbs and, reflecting on the rapid advances now being made in this field, encouraged all WHOCCs to continue to engage with the standards development processes now under way to ensure that such standards kept pace with commercial developments.

Dr Heidi Meyer began with an overview of PEI involvement in the revision of the WHO Guidelines on evaluation of biosimilars, adopted on the recommendation of the Committee in April 2022, and the WHO Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated)
to be submitted for consideration at the current meeting (see section 3.3.1 below). PEI had also provided support in the drafting of the new WHO guidance document on the development of a regulatory framework for human cells and tissues and for advanced therapy medicinal products, also scheduled for discussion at the current meeting (see section 3.1.1 below). PEI also continued to contribute to the ongoing revision of three other WHO written standards scheduled for submission to the Committee in 2023–2024.

With regard to WHO measurement standards, PEI had participated in several recent collaborative studies to support the development of international standards – several of which would be considered by the Committee at the current meeting. PEI had also continued in its efforts to support WHO regulatory systems strengthening activities, including through the provision of support in the further development of the WHO GBT to include blood regulation (GBT + blood), as well as participation in the corresponding benchmarking of NRAs. In addition, PEI had supported the African Vaccine Regulatory Forum in drafting and implementing vaccine-specific guidelines and in the development of related tools. PEI had also promoted the incorporation of these regulatory guidelines and tools into national regulatory environments through the holding of workshops.

Dr Meyer concluded by highlighting the support provided by PEI to the WHO prequalification programme for in vitro diagnostics (IVDs), most notably through the assessment of SARS-CoV-2 diagnostics for their suitability for WHO emergency use listing (EUL), the provision of guidance on the most appropriate unitage for use in HIV-1 nucleic acid amplification technique (NAT)-based assays, and support to Global Health Protection Programme workshops on IVD regulation.

2.3 Cross-cutting activities of other WHO committees and groups

2.3.1 Feedback from the 56th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations

Dr Herbert Schmidt updated the Committee on the outcomes of the 56th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) which had been held virtually from 25 April to 2 May 2022. The meeting had been productive, with six guidelines and 18 pharmacopoeial texts recommended for adoption. In addition, the ECSPP had recommended the establishment of 11 new international chemical reference substances to be distributed by the custodian laboratory, EDQM.

Dr Schmidt listed the above six guidelines, which all related to GMP, along with the other documents adopted at the meeting. Regarding the texts recommended for inclusion in the International Pharmacopoeia, Dr Schmidt noted that the monograph for medicinal oxygen had been revised and new monographs adopted for molnupiravir and molnupiravir capsules as part
of the WHO response to the COVID-19 pandemic. Monographs had also been adopted for maternal, infant, and child and adolescent health, including monographs for long-acting contraceptives and emergency contraception. The ECSPP had also recommended the adoption of monographs for antimalarial and antituberculosis medicines, including a monograph for isoniazid tablets that was the first such public standard developed for this important medicine. Dr Schmidt then summarized the additions that had been made to the catalogue of antiviral medicines, including important antiretrovirals, before concluding with a summary of the recommendations made by the ECSPP.

Noting the importance of its work, the Committee enquired as to how the ECSPP handled the overlap with biological medicines, and was assured that close contact was maintained with WHO colleagues working in this area, with topics of mutual interest discussed at internal WHO meetings and documents shared as necessary. By way of example, Dr Schmidt highlighted the common interest of both committees in reducing the use of animals in product testing.

2.3.2 Update from the WHO Product Development for Vaccines Advisory Committee

Dr Birgitte Giersing presented an overview of the recent activities of the WHO Product Development for Vaccines Advisory Committee (PDVAC). Throughout 2022, PDVAC had held virtual meetings to discuss specific priority diseases and related topics, including invasive non-typhoidal salmonella, Group A streptococcus and candidate mRNA vaccine selection. PDVAC was also currently leading an effort to partner with regions in identifying priority pathogens for vaccine development as part of the WHO Immunization Agenda 2030. PDVAC had been charged with recommending a shortlist of pathogen targets for new vaccines for endorsement by the Strategic Advisory Group of Experts on Immunization (SAGE) in April 2023.

With regard to specific product developments, Dr Giersing began by updating the Committee on a number of respiratory syncytial virus (RSV) immunization candidates now at an advanced stage of clinical development. These included long-acting mAbs such as nirsevimab, which had received a positive opinion from the European Medicines Agency in September 2022, as well as maternal vaccines for which the completion of Phase III trials was anticipated by October 2023. The current tuberculosis vaccine pipeline also included several candidate vaccines at an advanced stage of clinical development, and intended for use in adolescents and adults to boost waning immunity to BCG. In the context of this pipeline, PDVAC had advised WHO to develop a road map to identify the steps needed to prepare for vaccine introduction. Noting the progression of the recombinant fusion protein M72/AS01E candidate vaccine towards Phase III trials, Dr Giersing enquired as to when WHO written and
measurement standards might best be developed for such a product. Similarly, Dr Giersing wondered whether the existing WHO BCG vaccine guidelines would be adequate to support WHO prequalification of the next-generation BCG vaccines now in well-advanced clinical development, and what would be the trigger and process for updating such guidelines. Dr Giersing concluded by updating the Committee on the current status of enteric vaccine development and, observing that controlled human infection models (CHIM) for several diarrhoeal and enteric pathogens now existed or were in development, suggested that specific WHO guidance on the use of CHIM for enteric pathogens may also be needed.

Acknowledging the importance of the work carried out by PDVAC, the Committee enquired about the progress being made in developing human immunodeficiency virus (HIV) vaccines and universal influenza vaccines – both of which had been mentioned in previous PDVAC updates to the Committee. With regard to HIV vaccines, Dr Giersing reported that the results of a recent clinical trial had been disappointing and that a small Phase III trial was currently being conducted in men who have sex with men. The present HIV vaccine pipeline was sparse and no candidate vaccine was at an advanced stage of clinical development. Noting the suggestion to develop WHO guidance specifically on the use of CHIM for enteric pathogens, the Committee made reference to the WHO regulatory considerations document on human challenge trials for vaccine development adopted in 2016.

2.3.3 WHO prequalification and WHO emergency use listing

Dr Carmen Rodriguez-Hernandez updated the Committee on the cross-cutting issues of WHO prequalification (PQ) and WHO emergency use listing (EUL). Dr Rodriguez-Hernandez began by explaining that the former was an extensive review of product quality, safety and efficacy intended to underpin the decisions of procuring agencies, while the latter focused on a benefit–risk assessment of essential quality data during a public health emergency that was reviewed on a rolling basis. WHO EUL would result in a time-limited recommendation that, following further development, could lead to marketing authorization and WHO PQ.

Since 2002, a number of vaccine-specific PQ, EUL and other activities had been undertaken, and an emphasis was placed by Dr Rodriguez-Hernandez on the 11 diverse COVID-19 vaccines currently under WHO EUL. A number of WHO COVID-19 advisory groups had been involved in developing recommendations in relation to variant evolution, the impact of such variants on countermeasures such as vaccines, and the need for changes to vaccine composition and for booster doses. After taking into account such advice, SAGE then recommends policies and strategies for vaccine use. Following discussions
with regulators and the WHO Blueprint for Research and Development team, WHO guidance had also been revised to allow for EUL applications for COVID-19 vaccines based on immunobridging data. Although the revised guidance avoided being overly prescriptive, it was aligned with current WHO target product profiles (TPPs) for COVID-19 vaccines and with other related WHO resources and documents, and clearly sets out the considerations and requirements to be met using such an approach. Dr Rodriguez-Hernandez set out in detail the triggers, considerations and steps involved in transitioning COVID-19 vaccines from WHO EUL to WHO PQ.

Dr Rodriguez-Hernandez concluded by reviewing the main features, regulatory status and challenges of currently available mpox vaccines, which are based on live attenuated smallpox vaccines. The current WHO strategy was to request assessment of manufacturer dossiers by stringent regulators, make recommendations on vaccine use during emergency situations and support NRAs through resilience mechanisms. A number of actions in these areas had now been taken, including the drafting of legal documents.

Noting the importance of WHO PQ and EUL in the context of the ongoing COVID-19 pandemic, the Committee commented that despite WHO PQ some vaccines were still not approved in some regions. This suggested that further work was still needed and the Committee wondered if compliance might be a confounding issue. The Committee was informed that although WHO worked closely with reference regulatory authorities to avoid duplication of effort, it would sometimes conduct focused inspections – which were particularly challenging due to the quarantine requirements in some regions resulting from the pandemic. The Committee also enquired if all WHO EUL product manufacturers had committed to transitioning their products to marketing authorization and WHO PQ. In response, it was noted that although EUL is limited to 2 years, the situation was being complicated by a number of regulatory, cost and storage facility issues in some countries, particularly LMIC.

### 2.3.4 WHO International Nonproprietary Name Expert Group

Dr Raffaella Balocco updated the Committee on the recent activities of the WHO International Nonproprietary Name (INN) Expert Group, which assigns unique INN to medicinal substances, including biological substances. Since insulin human became the first recommended INN for a recombinant substance in 1982, the range of biological and biotechnological substances had increased in both size and complexity, with new stems being introduced for a range of novel protein constructs.

Dr Balocco highlighted the example of innovative mAbs, the systematic scheme for which had previously been based on the stem -mab. Following the proliferation of such products, significant reservations about the future suitability of this approach had resulted in the INN nomenclature scheme for
mAbs changing in 2021, with the stem -mab being discontinued and replaced by four new stems (-tug, -bart, -ment and -mig). Dr Balocco provided the Committee with a brief overview of how each of these new stems would be applied. In addition to these stems, infixes would also continue to be used in the mAb nomenclature scheme where they were informative and useful. Most such infixes remained unchanged.

Dr Balocco went on to review a number of naming issues arising from different COVID-19 vaccine developments. Historically, vaccines had been based on whole killed or live attenuated pathogens, subunits derived from pathogens or inactivated toxins, and had not been included in the INN system. However, some vaccines against infectious diseases had recently been developed based on recombinant DNA technology, including antigenic subunits produced in expression systems, recombinant DNA derived virus-like particles (VLPs), recombinant live vectors expressing heterologous antigens, and nucleic acid vaccines. As well-defined active ingredients, these fulfil the criteria for INN assignment. Similarly, peptide vaccines are chemically well defined and therefore also fall within the INN naming system. A COVID-19 vaccine tracker had now been compiled using detailed information on the development of individual COVID-19 vaccine candidates.

Dr Balocco concluded by drawing the attention of the Committee to the recently published INN Bio Review. This document is intended to be a regularly updated living resource providing an up-to-date inventory of the policies and policy decisions adopted by the INN Expert Group, and of the names assigned to biological products. Comments and suggestions from interested parties such as the Committee were encouraged.

The Committee expressed its reservations concerning the loss of the -mab suffix and wondered if this might lead to confusion where a change resulted in similar products having unrelated names. Assurance was given that already established names could not be changed and that several potential applicants and regulators had expressed their approval for the developments outlined.

2.3.5 WHO Model Lists of Essential Medicines

Dr Lorenzo Moja provided an overview of recent and planned activities in relation to the WHO Essential Medicines List (EML) and WHO Essential Medicines List for Children (EMLc). Both EML are used by a number of organizations working to improve access to safe, effective, good quality and affordable essential health products, including through the facilitation of informed procurement decisions.

---

The original EML was published in 1977 and listed 240 medicines – with the current 22nd edition now listing almost 500 products.

Dr Moja emphasized the crucially important concept of therapeutic equivalence in the EML, and the associated use of a square symbol to indicate similar clinical efficacy and safety within a pharmacological class. This enabled countries to select the most appropriate single medicine based on price, local availability and acceptability. This concept is equally important for biosimilars with regard to their therapeutic equivalence, interchangeability and switching. Guidance in this area is provided by the WHO Expert Committee on the Selection and Use of Essential Medicines. In its most recent guidance, this expert committee had recommended that although the use of the square symbol would be inappropriate for indicating alternative quality-assured biosimilars, the increased availability of such products could lead to greater market competition, improved access and reduced costs for patients and health systems. Listings for biological medicines on the EML should therefore include a separate note specifying that quality-assured biosimilars may be considered for selection at the country level. The expert committee had also made a number of recommendations regarding cancer medicines, including the WHO prequalified mAbs trastuzumab and rituximab. Although several new cancer medicines had been recommended for inclusion on the EML, a number of expensive products had not. Such highly priced medicines represent a significant problem and the expert committee had called for the establishment of a technical advisory group on pricing policies for medicines to provide evidence-based guidance on how to increase affordable access to essential and priority medicines. The expert committee had also reviewed evidence in support of the inclusion of CAR-T cell therapy for diffuse large B-cell lymphoma on the EML but citing concerns about cost and toxicity, had not yet made a formal proposal.

Dr Moja went on to inform the Committee that the recently updated WHO EML antibiotic companion document (AWaRe antibiotic book) would shortly be published with antibiotics against more than 30 infectious diseases included, along with recommendations on their use. The WHO AWaRe approach assigns antibiotics into one of three categories depending on the risk of resistance associated with their use. Developed between 2017 and 2019, this categorization scheme has been well received worldwide.

During discussion, the Committee enquired whether any cell and gene therapy products were currently on the EML and, if not, how they might be included. The Committee was informed that despite a number of standardization and cost challenges, CAR-T cell therapy would likely to be the first such product. Looking ahead, the complexity of such therapies meant that adopting a comprehensive approach without the addition of further expertise to the expert committee would be difficult. Given the enormous potential of such therapies, and the rapid pace of development, the Committee wondered if WHO could
adopt a more holistic approach to better coordinate and bring together all of the diverse committees and working groups currently working in this field.

Noting that despite being on the EML, some blood products remained unavailable in certain countries, the Committee also wondered if putting a medicine on the EML impacted upon its supply and availability at country level. The Committee was informed that although the EML was not particularly strong with regard to blood products, there was good evidence that each revision of the EML led to an increasing number of patients accessing new medicines. Noting that vaccine implementation was driven by SAGE, the Committee suggested that blood products might similarly benefit from more attention from the EML expert committee.

2.3.6  Risk–benefit assessment of antivenoms

Dr David Williams provided an update on the progress of the snakebite envenoming programme at WHO. In order to drive improved access to safe and effective treatments, a technical and scientific advisory group had now completed a set of four TPPs to guide the development of conventional animal plasma derived antivenoms for sub-Saharan Africa. These profiles were due to be published in late 2022, with additional TPPs for conventional animal plasma derived antivenoms for South Africa having also been drafted and scheduled for publication in 2023. TPPs for small-molecule inhibitors and engineered antibody therapeutics were also being developed.

Following the adoption of resolution WHA71.5 in 2018, which calls on WHO to ensure the quality and safety of snake antivenoms, WHO developed a risk–benefit assessment procedure for snake antivenoms. During 2022, this activity had been expanded to include North Africa, the Middle East and South Asia, with 17 products currently under evaluation. To support this work, WHO had developed a website on the risk–benefit procedure for antivenoms that details the status of applications and their outcomes. With the agreement of antivenom producers, GMP inspection reports and public laboratory assessment reports will also be published on this website following the completion of product evaluation. In addition, development of the snakebite information and data platform has continued and now includes country-level epidemiological data, as well as maps showing the prospective impact of climate change on the global distributions of venomous snake species. Finally, as part of the WHO antivenom stockpile programme, an initial landscape analysis and scoping project was now under way on a potential stockpile facility for sub-Saharan Africa, the next phase of which will examine the possibility of distributing and monitoring the use of antivenoms in eight West African countries. Depending on the project outcomes, the programme could be expanded to all sub-Saharan African countries and then to other regions.
3. International Recommendations, Guidelines and other matters related to the manufacture, quality control and evaluation of biological products

3.1 Cell, tissue and gene therapy products

3.1.1 Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products

Cell, tissue and gene therapy products are highly diverse and typically complex, with many developed to address otherwise unmet medical needs. Such inherent complexity presents regulators with significant challenges and although some countries have established regulatory frameworks and guidance for these products, there is currently a lack of harmonization between countries and regions. Regulatory oversight is crucially needed to encompass both immediate risks (such as infection) and longer term risks (such as oncogenic potential). At present, significant regulatory variations exist in relation to key areas such as terminology, the types and extent of product regulation, and the levels of regulatory oversight required for different types of product.

Previous international calls for harmonization had included resolution WHA67.20 adopted in 2014 and the recommendations of an International Conference of Drug Regulatory Authorities (ICDRA) meeting in 2018. As a result, this topic had already been the subject of previous discussions of the Committee, and in 2020 the Working Group on Cell and Gene Therapy Products established a drafting group to develop the outline contents of a potential WHO considerations document. During a series of informal meetings and public consultations, and following a number of highly positive comments, a consensus had been reached on the need for this project to continue. However, it was also felt that the increased citing of existing national and international resource documents was needed, along with the revision of terminology and greater clarity on the exact purpose and scope of the document.

The Committee was informed that the resulting document was intended to form part of a process of addressing the acknowledged need for harmonization in areas such as terminology and the use of risk-based approaches in effective regulatory decision-making. To this end, a table had been developed showing examples of different product types and their potential risks. A proposed “decision tree” on the classification and associated risk criteria of cell, tissue and gene therapy products had also been included, and the need for compliance with GMP, good laboratory practices and good clinical practices highlighted. It is hoped that the promotion of such a risk-based approach will encourage regulators to expand their capacities in this area, including through regulatory cooperation and reliance to better leverage limited resources more efficiently and effectively, improve regulatory harmonization and increase access to such products.
The Committee discussed the numerous challenges to be addressed during the development of WHO guidance on establishing regulatory frameworks for such highly diverse and complex products. There was agreement that issues of donor remuneration and donation ethics would not fall under the scope of this document as these were already covered in other WHO guidance. There was also acknowledgement that the precautionary principle, for example as applied to blood transfusion, may not be entirely applicable in this context as the associated risks were more difficult to categorize, with some minimally manipulated products potentially carrying substantial risks. The Committee agreed that a risk-based approach should be specifically highlighted in the document and further elaborated upon. The document should also clearly distinguish between the distinct concepts of low versus higher risk and known versus unknown risk. A distinction would also need to be made between manufacturing risks and therapeutic product use risks.

Acknowledging that the current document was urgently needed and represented a good first step in bringing various stakeholders together, the Committee proposed a number of further improvements and refinements for consideration during its further development. The Committee looked forward to discussing the revised outcome document at its next meeting in March 2023.

3.2 In vitro diagnostics

3.2.1 WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices

The regulation of medical devices is essential for assuring their quality, safety and performance. In 2014, the adoption of resolution WHA67.20 underlined the importance of effective regulation of medical products in strengthening health systems and improving public health. The WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices (GMRF) was published in 2017 to provide guidance to countries in developing regulatory controls for such devices. Driven by technological advances and the increasing complexity of medical devices, and by the need to support new developers and regulators with limited experience this field, a process of revision of the GMRF had been undertaken. Specific topics addressed in the revised document included updated guidance on post-market surveillance and on good reliance practices, and the recent integration of medical device indicators into the WHO GBT. In addition, the COVID-19 pandemic had highlighted the need for timely access to safe and reliable medical devices and IVDs authorized for emergency use.

The revision process had been led by a working group that included national regulators of medical devices, representatives of international harmonization initiatives and subject matter experts, with the overall process...
guided by a WHO steering group. Following a first round of public consultation, the draft document had been revised and then subjected to a second round of public consultation. The resulting document provides guiding principles and sets out the characteristics of effective regulatory systems for medical devices including IVDs that can be incorporated in law, with a particular focus placed on the responsibilities of legislators and NRAs. New or expanded guidance is provided in key areas such as the use of risk-based classification systems, the role of regulatory reliance and recognition, emergency use authorization and the regulation of donated devices. Efforts had also been made to better align the terminology used in the revised GMRF with other international initiatives in this area. Feedback received during public consultation had been positive, with the majority of suggestions now incorporated into the document.

While acknowledging the importance of the revised GMRF, and the considerable efforts of the working group, the Committee also raised a number of concerns. Specifically, the Committee felt that the terminology used in WHO guidance such as the GMRF should be aligned with internationally accepted definitions. In particular, the Committee noted that the internationally accepted definitions of “adverse event” and “serious adverse event” had not been used in the GMRF, and indicated that this issue should be addressed. The Committee further emphasized that, in addition to monitoring serious adverse events, it was important to monitor trends for all adverse events, as their frequency was also a potential concern and could trigger a review of product safety. The Committee also discussed whether the revised GMRF should now use the term “WHO-listed authority” to be consistent with guidance for medicines and vaccines. Regarding an issue raised during public consultation concerning the necessity for lot verification testing of medical devices, the Committee agreed that, although important, such a requirement should be based on an assessment of risk.

Addressing a concern that the GMRF may only be applicable in LMIC, assurance was given that all WHO written standards were advisory and intended to provide principles based on scientific review and expert consensus to all countries as a basis for setting regulatory requirements. The Committee noted that although the revised GMRF was a departure from the WHO recommendations and guidelines documents it typically reviews, it nevertheless aligned with other WHO guidance documents, specifically in relation to regulatory considerations, and was thus comparable to other WHO written standards adopted in the past.

Having reviewed the changes made to the text to address the concerns raised, the Committee recommended that the document WHO/BS/2022.2425 be adopted and annexed to its report (Annex 3).
3.3 **Vaccines and related substances**

3.3.1 **Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated)**

Oral poliomyelitis vaccines (OPVs) have been the mainstay of the Global Polio Eradication Initiative (GPEI) since its inception. The WHO Requirements for poliomyelitis vaccines (oral) were adopted in 1962 and have been updated on several occasions to take account of improvements in vaccine manufacture and quality control, as well as the significant progress made towards global polio eradication. The current WHO Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated) had been adopted in 2012. Since that time, a number of developments had taken place with potential consequences for the production and quality control of such vaccines. These developments included the introduction of more genetically stable poliovirus strains used to produce novel OPV (nOPV) to prevent the emergence of circulating vaccine-derived polioviruses, technological innovations such as the use of HTS technologies in the quality control of OPV, and the need to comply with evolving biocontainment requirements.

At its meeting in October 2020, the Committee had expressed its support for the revision of the current WHO Recommendations to address these and other developments, and to take into account recently published relevant WHO guidance. Following a WHO expert review of pertinent documents, including GPEI documents, a number of key issues had been identified for consideration. A first draft of the revised document had then been reviewed during a virtual WHO informal consultation held in November 2021 and attended by representatives from industry, regulatory authorities and other organizations involved in vaccine development and production. Following this, a second draft had been prepared and subjected to two rounds of public consultation before being finalized for submission to the Committee.

The revised Recommendations now covered issues such as: (a) the application of HTS technologies in quality control and their potential to replace in vivo neurovirulence testing in routine lot release; (b) removal of the rct40 test; (c) considerations in the development and quality control of vaccines using nOPV strains; (d) the use of non-pathogenic strains in neutralizing antibody assays during clinical studies; and (e) guidance on the clinical evaluation of safer nOPV strains that may be developed. The revised Recommendations had also been aligned with recently published WHO documents in this area to facilitate compliance with current polio eradication approaches.

The Committee noted that the use of HTS had previously been endorsed only for OPV3 quality control, and that the results of a collaborative study involving OPV1 and OPV2 were to be presented later in the meeting (see section 9.2.2 below). Acknowledging that HTS produces results consistent with data
obtained using the mutant analysis by polymerase chain reaction and restriction enzyme cleavage (MAPREC) test, the Committee welcomed the upcoming proposal to extend its use to OPV1 and OPV2 quality control. The Committee also enquired about the steps required to ensure the genetic stability of the safer nOPV strains of serotypes 1 and 3 now being proposed for use in OPV production. The Committee was informed that, as with nOPV2 strains, the serial passaging of such viruses indicated that they accumulate mutations more slowly than conventional strains. Further studies would be conducted to confirm their attenuation in transgenic mice followed by clinical studies.

The Committee then reviewed the revised document taking into account the issues that had been raised during both the WHO informal consultation and subsequent public consultations. Acknowledging that the introduction of guidance on HTS was an important aspect of the revised Recommendations, and noting the broad consensus among manufacturers and regulators regarding its advantages, the Committee welcomed the guidance now provided. The Committee noted a suggestion made by manufacturers and regulators that WHO considers developing further technical guidance on performing HTS along with training on HTS method development and validation to support the implementation of the revised Recommendations. The Committee noted that implementation workshops based on the revised WHO Recommendations would provide guidance and training for manufacturers and regulators on the use of HTS in the short term. The Committee also felt that it might be helpful to establish a central database to capture the collective experiences of manufacturers and to support the development of acceptance criteria. Noting that, in addition to OPV manufacture, HTS would undoubtedly be used for the quality control of other vaccines in future, the Committee further suggested that WHO consider establishing an HTS reference laboratory to support the implementation of HTS as a routine quality control technology.

The Committee discussed a number of further issues raised during public consultation, including the need for flexibility in the guidance on how long a single harvest should remain identifiable during testing, and on the selection of appropriate vaccine vial monitors during OPV shipping and distribution. After making a number of minor changes to the text, the Committee recommended that the document WHO/BS/2022.2423 be adopted and annexed to its report (Annex 2).
4. International reference materials – biotherapeutics other than blood products

4.1 WHO international reference standards for biotherapeutics other than blood products

4.1.1 First WHO International Standard for cetuximab

Cetuximab is a biotherapeutic mAb that binds to the extracellular domain of the human epidermal growth factor receptor (EGFR). It competes with endogenous epidermal growth factor (EGF) and transforming growth factor (TGF)-α, thus inhibiting EGFR downstream signalling and preventing cell proliferation. Cetuximab is administered by intravenous infusion as a monotherapy or combined with other chemotherapies in the treatment of KRAS wild type colorectal tumours and squamous cell carcinoma of the head and neck with over-expression of EGFR. The use of cetuximab has been associated with improved survival rates in metastatic colorectal cancer patients. A number of cetuximab biosimilars have also been developed and approved for use in some countries.

As with other mAbs derived through recombinant DNA technology, cetuximab is structurally complex and sensitive to small changes in the manufacturing process. Evaluation of its bioactivity in vitro is essential during product development and is routinely performed by the manufacturer for lot release using proprietary reference materials and bioactivity units. However, cetuximab products are dosed and labelled in mass units with no reference to its biological activity. An international collaborative study involving 22 laboratories in 12 countries had therefore been conducted to assess the suitability of a candidate material (NIBSC code 21/170) for use in calibrating bioassays routinely used to measure cetuximab activity, and to assign a set of values in units of biological activity per ampoule. Fifteen of the laboratories performed inhibition of proliferation (IOP) assays. In addition, the antibody-dependent cellular cytotoxicity (ADCC) activity of the preparation had been assessed by six laboratories using seven different assays, while a limited number of laboratories performed various FcγR binding assays, with one laboratory also including a C1q binding assay.

Study results indicated that the candidate material 21/170 was suitable for use as an international standard for harmonizing each of the different assay types used to determine cetuximab bioactivity. In addition, real-time stability data monitored over 14 months indicated no loss of activity when the candidate material was stored at either −20 °C or 4 °C; however, some loss of activity was noted at higher temperatures, especially when used in the ADCC assay. Applying the Arrhenius equation, a degradation rate of 0.075% per year was predicted for the ADCC assays when the material was stored at the recommended
temperature of −20 °C. However, more stability data was needed with regard to EGFR binding and IOP activity.

The Committee sought clarification on the recommended storage and shipping temperatures for the prospective international standard and were informed that it should be stored at −20 °C but could be safely shipped at ambient temperature. The Committee also asked for more detail on the suitability of the candidate material for different types of assays. It was clarified that for some binding assay formats, relatively few tests had been performed in the collaborative study, and the low affinity of the material meant that for certain assays there was insufficient material in the ampoule to obtain a full dose–response relationship. Consequently, the suitability of the material could not be assured for use in such formats. The Committee was assured that the material was suitable for ADCC reporter-gene assays.

The Committee considered the report of the study (WHO/BS/2022.2429) and recommended that candidate material 21/170 be established as the First WHO International Standard for cetuximab with an assigned unitage of 1000 IU/ampoule for IOP activity, 1000 IU/ampoule for ADCC activity, 1000 IU/ampoule for EGFR binding activity, 1000 IU/ampoule for FcγRIIIa(V158) binding activity and 1000 IU/ampoule for FcγRI binding activity. Noting that this material was intended to support bioassay development and define IU of bioactivity for the purposes of assay harmonization, the Committee emphasized that it was not intended to define the specific activity of cetuximab products or to serve as a reference product for biosimilarity determination or dosing requirements.

4.1.2 First WHO International Reference Panel for antibodies to infliximab

Infliximab is an anti-tumour necrosis factor (TNF) chimeric mAb used to treat a range of autoimmune disorders, including rheumatoid arthritis, Crohn's disease, ulcerative colitis and psoriasis. Following the expiry of the original patent in 2013, several infliximab biosimilars had now been approved worldwide, thus reducing costs and improving patient access. Despite the clinical benefits of TNF inhibitors, a proportion of patients fail to respond, fail to maintain a response following initial improvement or experience adverse events that ultimately restrict treatment. Given its potential involvement in ineffective treatment outcomes and clinical sequelae, unwanted immunogenicity is an important concern in the clinical setting.

Published evidence suggests that the frequency and level of anti-drug antibodies (ADAs) varies between studies, and is affected by the sampling times and assay platforms used. In some infliximab-treated patients, drug levels are sufficiently high and despite ADA formation, contribute to clinical remission – while in other patients, ADAs decrease drug levels and lead to treatment failures. Some clinical laboratories have therefore implemented the clinical monitoring of
ADA and drug levels to guide dose selection and frequency of administration – and even to potentially allow for switching to another biotherapeutic to ensure optimal treatment – by employing commercial kits or methods developed in house. However, other such laboratories remain cautious due to conflicting or noncomparable results, often due to the use of assays with different characteristics and to the current lack of standardization. There is consequently a recognized need to standardize ADA testing across different analytical assay platforms and laboratories through the provision of suitable reference materials for use as positive controls. The First WHO International Reference Panel for antibodies to erythropoietin (human) had been established in 2015 to assess the performance of ADA assays, and a similar approach had been taken in preparing an international reference panel for use in assays for detecting antibodies to infliximab.

An international collaborative study involving 17 laboratories in 11 countries had been conducted to evaluate two lyophilized antibody candidate materials (NIBSC codes 19/232 and 19/234) for use as international reference materials. The aims of the study had been to: (a) evaluate the two antibodies against infliximab across the range of available assays and assess their suitability for use as performance indicators; and (b) assign an arbitrary unitage to each material to enable the calibration of local standards and assay harmonization. The majority of assays used (n = 18) were based on antibody binding, with four neutralization assays also used. Study results indicated that two lyophilized antibody preparations would be suitable for use as a prospective First WHO International Reference Panel for antibodies to infliximab. Compared to in-house standards, inter-laboratory variability was reduced and geometric mean estimates for ADA levels remained largely consistent when candidate material 19/234 was used as a common standard for the quantitation of ADA levels in different samples. The degree of harmonization was however largely dependent on assay type, sample and laboratory.

Characterization of the two antibodies demonstrated that they were distinct not only in terms of isotype but also in their affinity and dissociation profiles. Candidate material 19/234 is a high-affinity immunoglobulin G1 antibody that binds strongly in different assay types while 19/232 is an IgG4 antibody exhibiting variable binding activity and a fast dissociation rate. Accelerated thermal degradation studies indicated that both candidate materials were stable for at least 22 months when stored at up to 20°C. In addition, reconstituted samples were stable at 4°C after 1 week and could be freeze-thawed without loss of activity.

Noting that ADAs were of diverse IgG isotypes and that IgG4 was more representative of a mature (that is, chronic) response, the Committee recognized the importance of detecting all isotypes, thus underlining the need for both reference materials for use in clinical monitoring to promote better patient outcomes. The Committee considered the report of the study (WHO/
and recommended that candidate materials 19/234 and 19/232 be established as the First WHO International Reference Panel for antibodies to infliximab. The Committee further recommended that the candidate material 19/234 serve as a common standard for assay characterization and calibration of in-house and commercially available anti-infliximab antibody preparations with an assigned unitage of 50,000 IU/ampoule for both binding and neutralizing antibody activities. No units were assigned to the reference material 19/232.

4.1.3 Second WHO International Standard for interleukin-6 (human, recombinant)

Interleukin-6 (IL-6) is a pleiotropic cytokine secreted by multiple cell types during infection, inflammation or cancer. It mediates both pro- and anti-inflammatory effects that are critical in regulating B-cell and T-cell responses, and for coordinating both innate and adaptive immune responses. The aberrant production or dysregulation of IL-6 results in chronic inflammation, autoimmune disorders and malignancies. Consequently, IL-6 and its binding components are key targets for clinical intervention in various indications with several anti-IL-6/anti-IL-6 receptor therapeutics either approved or in development.

The First WHO International Standard for interleukin-6 (human, recombinant) had been widely used as a primary standard for the calibration of IL-6 preparations used in various applications, and for the calibration of immunoassays measuring IL-6 levels as a biomarker of inflammation or disease pathology in clinical settings. As a result of its diverse range of applications there has been a consistently high level of demand for this international reference standard and stocks are now depleted. In October 2021, the Committee had endorsed a proposal for its replacement.

A recombinant human IL-6 preparation, expressed in E. coli had therefore been procured from a commercial supplier and formulated in a phosphate-based buffer, filled and lyophilized. The resulting candidate material (NIBSC code 21/308) had then been assessed for its suitability to serve as a reference standard in an international collaborative study involving 15 laboratories in seven countries. The biological activity of the candidate material had been measured using a range of routine bioassays and calibrated relative to the current international standard. In-house testing revealed that when reconstituted in water, repeated freeze-thawing affected the activity of the IL-6 preparation. Consequently, the study protocol included samples reconstituted in water and in phosphate-buffered saline supplemented with 0.1% bovine serum albumin. Study results indicated that, independent of the assay selected, the use of the candidate material resulted in acceptable parallelism and intra- and inter-assay variability. The data also indicated acceptable parallelism between the study samples and the current international standard. The geometric mean estimate of IL-6 bioactivity of candidate material 21/308 relative to the current
international standard was calculated to be 143 424 IU/ampoule based on data from both bioassays and immunoassays (95% CI = 135 539–151 769). Comparisons of potency based on reconstitution practice indicated that 10 laboratories following the revised protocol observed a significant difference between coded duplicates of the candidate replacement material when using reporter gene and immunoassays but not proliferation assays. Eight laboratories following the original protocol reported no difference regardless of assay method. Users will therefore be advised to reconstitute the standard in water in the IFU.

Accelerated thermal degradation studies carried out over 6 months indicated that the candidate material was sufficiently stable to serve as an international standard, with ongoing stability monitoring now under way to confirm such stability and predict degradation rate. Additional studies indicated that the candidate material was stable for at least 1 week following reconstitution when stored at either 4 °C or 20 °C. Freeze-thawing after reconstitution reduced IL-6 activity and was therefore not recommended.

The Committee considered the report of the study (WHO/BS/2022.2436) and recommended that candidate material 21/308 be established as the Second WHO International Standard for interleukin-6 (human, recombinant) with an assigned unitage of 143 000 IU/ampoule.

4.2 Proposed new projects and updates – biotherapeutics other than blood products

4.2.1 Proposed Second WHO International Standard for serum amyloid A

Serum amyloid A is a marker of acute phase inflammation and is useful for monitoring such inflammation as its levels rise rapidly following an inflammatory stimulus but quickly return to normal following resolution of the event. The current First WHO International Standard for serum amyloid A has been available for almost 30 years and is used to calibrate immunoassays. Despite being assigned an IU, this value is an arbitrary conversion derived from measurements in SI units (1 μg = 1 mIU) and the material is generally used to calibrate assays in SI units. Although sales of the current international standard had been relatively low for many years, recent notable increases have led to a demand of around 250 ampoules per year. This level of demand had resulted in the rapid depletion of stocks which, despite limits being placed on the number of ampoules per shipment, were expected to be completely exhausted within 18 months. Ensuring the continued provision of support to immunoassay development, calibration and harmonization in this area will necessitate the preparation of a replacement international standard. It was expected that such a standard would continue to be used by the manufacturers of serum amyloid A immunoassays, as well as by clinical and quality control laboratories.
As the current international standard is serum-derived, it is proposed that the replacement should also be a serum-derived material based on clinical remnant samples with high serum amyloid A levels donated by the same source. Both the candidate material and the current international standard would be evaluated by at least 10 laboratories using immunoassays. Based on the resulting data, the suitability of the candidate material to serve as an international standard would be assessed and a unitage assigned relative to the current international standard. Serum and plasma samples covering a range of serum amyloid A concentrations would be included to assess the commutability of the candidate material. An accelerated thermal degradation study would be carried out by selected laboratories. The anticipated batch size was 3000–5000 ampoules. It was anticipated that the collaborative study outcomes would be submitted for consideration by the Committee in 2024.

The Committee sought clarification as to whether the assigned unitage of the replacement international standard would be in SI units or IU. Clarification was given that the final decision on this would depend on the data returned by study participants and whether the same conversion factor could be applied. Given that current assay kits are calibrated in SI units, this was assumed to be the best approach and was unlikely to negatively affect users. Ultimately, it may be better to assign SI units based on a primary method of measurement, such as mass spectroscopy. The Committee noted that this was a good example of replacing a legacy international standard to which users had inappropriately assigned SI units. As it would be inappropriate to leave users without a reference standard, the Committee endorsed the proposal (WHO/BS/2022.2439) to develop a Second WHO International Standard for serum amyloid A. The Committee would consider the question of unitage assignment once the outcomes of the collaborative study had been presented.

4.2.2 Proposed First WHO International Reference Panel for the characterization of crystallizable fragment domain interactions

The number of approved biotherapeutic mAbs and other biological products bearing a crystallizable fragment (Fc) domain continues to increase, with the majority of such products being developed to treat cancer or immune-related disorders. Interest in these products is being driven by improved understanding of disease targets and by the clinical success, specificity, stability, long half-life and relatively good safety profile of such products. Human immunoglobulins have two functional domains, namely, the antigen binding fragment (Fab) domain responsible for antigen specificity and the Fc domain which mediates antibody effector functions and which therefore plays an important role in determining product therapeutic activity and safety. Although the relationship between Fc domain structure and function is well recognized, the relative contribution
made by various Fc domain interactions and associated effector functions to the clinical effects of mAb products remains unclear. As characterization of the Fc domain and of Fc domain effector functions must be controlled as critical quality attributes, a range of methods continues to be developed for this purpose, including biochemical and cell-based assays.

The proposed panel would help to address a need to support the development, performance assessment, qualification and validation of Fc domain binding assays. A panel of reference reagents consisting of mAbs and other proteins bearing Fc domains and covering different Fc domain characteristics will be developed. The materials for the panel are expected to be obtained either as donations from manufacturers or through collaboration with other institutions. In some cases, materials may also be produced in house or purchased as required. It is envisaged that the suitability of the candidate panel materials will be assessed in an international multicentre collaborative study comparing their relative bioactivity and performance in as many assay platforms as possible.

The Committee commented that the proposed panel was unusual with regard to biological standardization insofar as it would consist of different molecules for use with a range of different assays. Normally, the Committee would assign unitages to a particular type of molecule for use in certain types of assay. Clarification was given that the proposed panel was intended to be used to characterize a diverse range of products containing Fc domains and would not be used to assign units of biological activity. The Committee recommended that while developing the panel, careful consideration should be given to the impact of post-translational modifications (such as glycosylation) on Fc domain interactions and functions, and that appropriate expert collaborations should be sought. Acknowledging the potential challenges associated with sourcing the various materials and the proposed timeline, the Committee endorsed the proposal (WHO/BS/2022.2439) to develop a First WHO International Reference Panel for the characterization of crystallizable fragment domain interactions.
5. International reference materials – blood products and related substances

5.1 WHO international reference standards for blood products and related substances

5.1.1 Second WHO International Standard for blood coagulation factor XIII (plasma)

Blood coagulation factor XIII (FXIII), or fibrin stabilizing factor, is a transglutaminase that circulates in plasma and functions by cross-linking fibrin to stabilize its structure. FXIII is a heterotrimer consisting of two A and two B subunits in a 1:1 ratio, with excess FXIII-B circulating in free form. The First WHO International Standard for blood coagulation factor XIII (plasma) was established in 2004 and is used as a reference standard in the measurement of FXIII potency in patient plasma to diagnose FXIII deficiency, as well as in plasma-derived and recombinant therapeutic concentrates and fibrin sealants. Due to continuing demand from hospitals, clinical laboratories, manufacturers of plasma products and assay kits, and regulatory authorities, stocks of the current international standard are running low and will be exhausted by the end of 2022.

An international collaborative study involving 13 laboratories in seven countries was undertaken to calibrate a candidate material (NIBSC code 20/292) for both its activity and A2B2 antigen and total FXIII-B subunit levels against the current international standard. The study also investigated the relationship between FXIII measurement in a concentrate preparation and in a plasma standard. The candidate material was prepared from a pool of 20 normal donors and all laboratories were requested to use their normal routine assay methods for FXIII activity and A2B2 antigen estimation, while using the recommended ELISA specific to the total FXIII-B subunit.

Potency estimates for the candidate material using duplicate samples for testing showed good inter-laboratory agreement (combined geometric coefficient of variation (GCV) = 3.8%; and combined geometric mean FXIII potency = 1.04 IU/ml). Estimated FXIII A2B2 antigen level also showed good inter-laboratory agreement (combined GCV = 4.8%; and combined geometric mean value = 0.98 IU/ml). Estimates of total FXIII-B subunit levels also showed good inter-laboratory agreement (combined GCV = 5.3%; and combined geometric mean value = 0.92 IU/ml). No evidence was found of consistent non-parallelism for the overall study. Assays of the concentrate preparation for FXIII activity also showed good agreement (overall GCV = 8.7%) indicating that a plasma standard would be suitable for measuring FXIII concentrates. Further analysis demonstrated good stability of the candidate material, with only negligible loss (0.001%) in FXIII potency at the storage temperature of −20 °C based on a 17 month storage
Discussion centred on the number of laboratories that had been contacted and the percentage of these that had eventually participated. It was acknowledged that the COVID 19 pandemic had disrupted both sample transport and the rate of laboratory participation. Participation had been voluntary and coordinated through the International Society of Thrombosis and Haemostasis (ISTH). The mix of accredited and non-accredited laboratories that had participated reflected the situation in hospitals performing this assay. Despite relatively fewer participating laboratories, the results and data obtained had been reassuringly robust and consistent with the previous international standard. The suitability and activity and antigen potencies of the candidate material had been endorsed not only by the study participants, but also by members of the FXIII & Fibrinogen Subcommittee of ISTH/SSC, ISTH/SSC Experts, the WHO-ISTH Liaison Group and the SSC Board.

Commenting on the selection of participating laboratories and on the final number of participants, the Committee suggested that choosing only accredited laboratories and defining an optimum number of laboratories for statistical power at the outset might have proved helpful. The Committee considered the report of the study (WHO/BS/2022.2438) and recommended that the candidate material 20/292 be established as the Second WHO International Standard for blood coagulation factor XIII (plasma) with assigned unitages of 1.04 IU/ampoule for overall potency, 0.98 IU/ampoule for A2B2 antigen content and 0.92 IU/ampoule for total FXIII-B subunit content.

6.1 WHO international reference standards for cell, tissue and gene therapy products

6.1.1 WHO international reference reagents for the quantitation of lentiviral vector copy number – amendment

The First WHO International Reference Panel for lentiviral vector copy number was established in 2019. The panel comprised three separate international reference reagents with values assigned in lentiviral (LV) copies/cell. Subsequent use of these international reference reagents revealed significant discrepancies in the data obtained using quantitative polymerase chain reaction (qPCR) and data obtained using droplet digital polymerase chain reaction (ddPCR) assays. These discrepancies were attributed to inherent technological variations between the two methods that could not easily be resolved. Additionally, it was noted that use of the chosen unitage (LV copies/cell) could limit the applicability of the reference reagents, and that removing reference to a single housekeeping gene would provide greater flexibility to end users when deriving cell numbers.

At its meeting in March 2022, the Committee had agreed in principle to a proposal to disestablish the First WHO International Reference Panel for lentiviral vector copy number and to instead develop two separate WHO international reference reagents, each with value assignments in LV copies/ampoule, subject to the submission of further supporting data. The Committee was updated on the further analysis and characterization of the two candidate materials (NIBSC codes 18/132q and 18/132d) that had now been completed. Thirty one laboratories in 13 countries had returned data on the two candidate materials, and evaluations had been made of their suitability to serve as WHO international reference reagents for lentiviral vector copy number for use with qPCR (candidate material 18/132q) and ddPCR (candidate material 18/132d). Confirmation was provided that both candidate materials had been derived from the same material and were intended for use alongside the previously established WHO International Reference Reagent for lentiviral vector integration site analysis (NIBSC code 18/144) which would remain in use as a standalone qualitative reference reagent for integration site analysis based on confident detection of the 10 defined integration sites, and intended for the validation of end user integration-site study protocols.

Discussion centred on the necessity of having two reference reagents, especially as these had been derived from the exact same material. The Committee was informed that it was now considered more appropriate to have two separate reference reagents as these were both assigned absolute values and the differences, though small, were significant. Currently, both qPCR and ddPCR
were being used and there was therefore a need for separate reagents until one method superseded the other entirely. The observed discrepancies were due to the different methodologies and not to the lentivirus.

The Committee considered the report of the study (WHO/BS/2022.2433) and, noting that copy number was an absolute rather than an arbitrary value, recommended that: (a) candidate material 18/132q be established as the WHO International Reference Reagent for the quantitation of lentiviral vector copy number by quantitative PCR, with an assigned value of \(6.89\ log_{10}\ copies/ampoule\) (95% CI = 6.81–6.98 \(\log_{10}\)); and (b) candidate material 18/132d be established as the WHO International Reference Reagent for the quantitation of lentiviral vector copy number by digital PCR, with an assigned value of \(6.75\ log_{10}\ copies/ampoule\) (95% CI = 6.71–6.79 \(\log_{10}\)). The Committee further recommended that the WHO International Reference Reagent for lentiviral vector integration site analysis, established in 2019, should remain available for use as a standalone qualitative reference reagent for integration site analysis.

6.2 Proposed new projects and updates – cell, tissue and gene therapy products

6.2.1 Proposed WHO international reference reagents for flow cytometry analysis of mesenchymal stromal cells and pluripotent stem cells

The quality control of cell therapy products currently relies on the use of in-house reference standards that exhibit significant batch-to-batch variation, with resulting major challenges in their sourcing and control. In addition, flow cytometry – one of the most commonly used techniques for evaluating cell therapy products – is prone to technical variation. The establishment of WHO international reference reagents for cell therapies would increase confidence in critical quality measurements, facilitate regulatory compliance and promote international regulatory harmonization. Such reference reagents would also facilitate the validation of internal reference standards, and the qualification and validation of release assays.

The mesenchymal stromal cell (MSC) field is highly active, with more than 1000 clinical trials under way, including trials of products for auto-immune diseases, graft versus host disease, osteoarthritis and chronic obstructive pulmonary disease. These multipotent stem cells are found in different tissues throughout the body and mediate immune modulation and tissue repair. Pluripotent stem cell (PSC)-derived cell therapies also represent a novel treatment approach for currently incurable diseases such as Parkinson's disease and age-related macular degeneration, and this field too is also rapidly expanding. Currently there are no standards or reference reagents available either for MSC-based therapies or for PSC-derived therapies.
The proposed WHO international reference reagents for flow cytometry analysis of MSC identity are aligned with the minimal criteria for defining MSCs as set out by the International Society for Cellular Therapy (ISCT). In 2018–2019, a successful WHO collaborative study had been conducted in which fixed, freeze-dried MSCs derived from human PSCs had been distributed to collaborators and tested for MSC markers using their in-house flow cytometry protocols. The results obtained had been highly consistent between participants, and reflected the expected expression of positive and negative markers, thus complying with ISCT identity requirements. However, such reference reagents were largely expended during the single collaborative study and facilities for scaling up production were not available. However, since then, evaluation of a revised procedure based on scalable sources of cells has been undertaken. Preliminary data comparing primary, umbilical cord derived MSCs, the readily expandable human fibroblast MRC-5 cell line and the human PSC-derived MSCs indicate that the biological and technical replicates used were broadly consistent. These results would seem to support the use of MRC-5 cells to develop an MSC reference reagent. Efforts are also under way to harmonize and achieve transparency around the manufacturing and quality parameters required to produce clinical grade PSCs. The proposed WHO international reference reagent for flow cytometry analysis of PSC identity would streamline these efforts, allow comparison between PSC lines and promote consensus in quality assurance.

In the case of both the MSC and PSC reference reagents, the proposed approach was to produce a master cell bank of 200–300 vials, followed by 3–5 independent working banks that would be used to produce 200–300 distribution vials for use in flow cytometry assessments in a collaborative study. It was anticipated that the completion of the production and quality control steps of the master cell bank and successive working cell banks would be followed by the distribution of study vials by September 2023, with the collaborative study expected to be completed by January 2024.

During discussion, it was highlighted that that MSCs are an inherently heterogenous group of cells and can be derived from multiple sources. There may therefore be a need to derive source-specific MSCs when creating the master cell bank. In addition, caution was urged in using only the flow cytometric aspects of the ISCT criteria for defining MSCs as these alone do not fulfil their definition criteria set. It was therefore recommended that functional correlates should also be taken into consideration. There was also a concern that end users may start to define a cell type as an MSC based solely on flow cytometric results obtained using WHO international reference reagents. The Committee was reassured that functional correlates would also be investigated. The intention of MHRA was to expand the programme to include reference
reagents for impurity analysis of cell therapy products while also considering the use of functional assays, such as those based on immune suppression.

Noting the importance of the field and the increasing use of MSCs and PSCs in clinical trials, the Committee endorsed the proposal (WHO/BS/2022.2439) to develop WHO international reference reagents for flow cytometry analysis of mesenchymal stromal cells and pluripotent stem cells.
Chikungunya fever is caused by the chikungunya virus (CHIKV) and is characterized by fever and severe joint pain. Although chikungunya fever has a relatively low mortality, with a case fatality rate in the region of 0.1%, significantly higher rates are observed in certain populations, particularly the elderly and those with comorbidities. First reported in 1952 in the United Republic of Tanzania and endemic in parts of Africa, chikungunya fever epidemics also often occur in Asia. In recent years, significant geographical expansion has taken place with over one million cases having been reported in Central and South America since 2014, and outbreaks recorded in southern Europe in the last decade. CHIKV shares the same mosquito vectors as dengue and Zika viruses, with the clinical presentations of the three diseases being very similar. The ability to discriminate between these diseases is very important and CHIKV infection is diagnosed either using NAT-based assays or by detecting CHIKV antibodies in patient serum.

Currently, no antiviral drugs are available to treat CHIKV infection and there is no licensed vaccine. However, several prospective vaccines are in development, with evidence suggesting that the level of neutralizing antibodies is an important correlate of protection. A workshop held in 2018 identified a number of challenges hampering vaccine development, including: (a) a lack of standardization of the assays used for clinical diagnosis; (b) a lack of reference materials needed to standardize neutralization assays; and (c) the need to define a protective level of neutralizing antibodies.

An international collaborative study had been conducted involving 26 laboratories in 12 countries to assess the suitability of two CHIKV antibody preparations to serve as a WHO international standard. The first candidate material (NIBSC code 1502/19) consisted of a lyophilized anti-CHIKV plasma preparation comprising a pool of three donations from the same recovered patient. The individual plasma donations had tested positive for CHIKV antibodies, and negative for other alphavirus antibodies and for dengue virus and Zika virus antibodies. The second candidate material (NIBSC code 1504/19) had been produced from pooled plasma from 10 CHIKV antibody-positive blood donations. Both candidate materials were included as duplicate samples to evaluate inter- and intra-assay variability. Additional samples included clinical plasma samples of differing CHIKV antibody titres to investigate commutability as well as samples containing antibodies to other viruses to investigate specificity. A range of both virus neutralization and antibody binding assays were used (both commercial and in-house). Virus neutralization data were returned by 16 laboratories and ELISA data by 15 laboratories. Both candidate materials
were consistently detected by all study participants, with intra-assay variation lower than inter-assay variation. Both candidate materials harmonized all of the virus neutralization and immunoassays used, with both performing equally well and exhibiting similar potencies. Both candidate materials were stable under the recommended storage conditions of at or below −20 °C and were considered suitable for long-term use. In addition, no significant reduction in antibodies was observed after 3 months incubation at 20 °C, thus supporting their shipment at ambient temperatures.

It was proposed that candidate material 1502/19 be selected for use due to the larger number of vials available and the absence of antibodies to other arboviruses (though the presence of such antibodies did not affect the performance of candidate material 1504/19). The principal envisaged use of the proposed international standard would be the calibration and harmonization of serological assays used for the quantification of anti-CHIKV neutralizing IgG, with a secondary use as a reagent to control immunoassay performance. It was further proposed that candidate material 1504/19 be reserved as a replacement batch for 1502/19 or used as a secondary standard with no unitage assigned. Although it was considered possible to correlate a defined protective level of neutralizing antibody (defined in IU) with a surrogate marker that could be measured by an alternative type of immunoassay, further studies would be required to conclusively establish such a relationship.

Reflecting on the prospective demand from vaccine manufacturers and researchers, discussion centred on the need for a secondary standard. However, the Committee agreed that WHO did not normally establish secondary standards and that the onus would be on major users to establish their own reference materials. The Committee considered the report of the study (WHO/BS/2022.2434) and recommended that candidate material 1502/19 be established as the First WHO International Standard for antibodies to chikungunya virus with an assigned potency of 500 IU/vial.

7.2  Proposed new projects and updates – in vitro diagnostics

7.2.1  Proposed First WHO International Standard for HIV-1 p24 antigen

The First WHO International Reference Reagent for HIV-1 p24 antigen was established in 1992 to enable the reliable comparison of p24 antigen assays both within and between laboratories. The detection of p24 antigen remains important today, especially in LMIC, with the international reference reagent now used by in vitro diagnostic manufacturers to ensure the analytical sensitivity of fourth generation combination assays. The Common Technical Specifications published by the European Union set out additional requirements for such assays, including the requirement that an IVD medical device must detect p24 antigen with a sensitivity of at least 2 IU/mL. Due to increasing demand, stocks
of the current international reference reagent are now low and expected to be exhausted within a year.

A recombinant p24 (rp24) protein was therefore purchased and evaluated against the current international reference reagent using a wide range of immunoassays. The potency of the material was found to be high, with all assays showing good linearity and parallelism. It was noted however that Abbott platforms gave lower potency estimates. The results of a small freeze-dry trial indicated only small losses in activity, with degradation studies not showing any significant losses after 4 weeks. A VLP had also been produced using an established method to mimic the First WHO International Reference Panel for HIV-1 p24 antigen, established in 2018. The subtype B sequence was selected and tested in a smaller number of assays. Historic data for subtype B samples from the international reference panel study were in good agreement and supported the use of the proposed VLP approach, with a pilot degradation study indicating good stability of the proposed material.

Although the rp24 was found to be suitable for most assay systems, it was of an unknown subtype, exhibited the above discrepancy using Abbot platforms and may prove problematic with regard to maintaining continuity of the IU in some platforms. The subtype B VLP performed well in initial testing, appears to be very stable, and would be easy to replace as it was produced internally. As a result, the VLP material will be assessed in an international collaborative study as the potential replacement for the current international reference reagent. The collaborative study will involve 10–20 participants, with the rp24 and a clinical sample included in the study. The proposed standard was expected to demonstrate superior analytical sensitivity and based on current demand it was expected that the 5000 vials would last for 20–30 years. It was anticipated that submission of the collaborative study report for consideration by the Committee would take place in late 2023.

Following clarification of the nomenclature to be used for the replacement standard, the Committee agreed that the VLP material met the necessary criteria for further evaluation. Agreement was also expressed with the proposed use of a clinical sample in the study, and a suggestion made to include at least one subtype C sample. A query was raised as to why VLPs were being used instead of cell culture and clarification given that this was due to the difficulty of growing sufficient virus numbers in cell culture.

The Committee endorsed the proposal (WHO/BS/2022.2439) to develop a First WHO International Standard for HIV-1 p24 antigen.

7.2.2 Proposed Third WHO International Standard for protein S (plasma)
Protein S is a vitamin-K-dependent plasma protein that acts as a cofactor in the anticoagulation function of protein C. The three analytes associated with the international standard are functional activity, free antigen and total antigen.
The primary uses of the standard are to support the diagnostic measurement of protein S levels in patients and to assign functional protein S values to therapeutic products such as virus-inactivated fresh frozen plasma and some prothrombin complex concentrates. Following steady demand, stocks of the Second WHO International Standard for protein S (plasma), established in 2006, are expected to be exhausted within 2 years.

It was proposed that a candidate replacement material would be sourced from the UK Blood Service in 2022 followed by an international collaborative study in 2023 involving around 30 laboratories. It was anticipated that the results of the study would be presented for agreement at the International Society for Haemostasis and Thrombosis prior to their submission for consideration by the Committee in 2023–2024. Based on current levels of usage, the proposed batch size of 8000 ampoules would be expected to last for 20 years.

During discussion, the potential issue of ensuring sample transport across borders and jurisdictions in the face of current import restrictions and other factors was raised. It was suggested that WHO might help address this issue, thereby increasing the number and quality of participating laboratories. There was also discussion concerning the desirability of establishing the minimum and optimum number of laboratories for any such study. It was noted that this issue is often discussed but is associated with a number of practical difficulties, including most recently the limitations placed on participation due to the COVID-19 pandemic. Although potentially beneficial, it remains difficult to set fixed rules concerning the number of study participants and their worldwide distribution, and instead a focus is placed on the consistency of results and appropriate statistical analysis. The Committee also enquired as to the methodologies that would be used for the testing and how these would be determined. The Committee was informed that the test methodologies would be developed by manufacturers, and that, despite being useful, performing a sub-analysis of the different methodologies used would be restricted by the number of participating laboratories.

The Committee endorsed the proposal (WHO/BS/2022.2439) to develop a Third WHO International Standard for protein S (plasma).

8.1 WHO international reference standards for use in public health emergencies

8.1.1 First WHO International Standard for SARS-CoV-2 antigen

Since the onset of the COVID-19 pandemic in March 2020 more than half a billion confirmed cases of infection with SARS-CoV-2 have been reported worldwide, including more than 6 million deaths. Diagnostic testing and contact tracing have been critical elements of national prevention and control strategies. Although NAT-based assays are the recommended “gold standard” approach for virus detection they are generally dependent upon the availability of expensive equipment and trained operators, thus making them less accessible in low-resource settings. In this context, the development of rapid diagnostic tests (RDTs) based on antigen detection has been a key part of the WHO-coordinated global research road map. In particular, there has been unprecedented demand for lateral flow devices that are inexpensive and easy to use at home or in community settings. Most antigen tests use nasopharyngeal or nasal swab specimens, with others using saliva or oral swabs. Although most such tests target the nucleocapsid (N) protein, a small number target the spike (S) protein or a combination of the two. Only limited comparative performance data have been published for SARS-CoV-2 antigen tests. Improved harmonization of data reporting would allow for the comparative assessment of such tests.

A proposal to develop a First WHO International Standard for SARS-CoV-2 antigen with an assigned potency in IU had been endorsed by the Committee in December 2020 to allow for evaluation of analytical sensitivity using a common reference and for the reporting of limits of detection in IU. Following a pilot collaborative study using a range of antigen tests, a potential candidate material (NIBSC code 21/368) had been identified and subsequently evaluated in an international collaborative study involving 31 laboratories in 14 countries. The candidate material consisted of lyophilized and formaldehyde-inactivated SARS-CoV-2 (Omicron sub-lineage BA.1) virus propagated on Vero cells and was evaluated as part of a panel of nine samples using 18 different SARS-CoV-2 antigen detection tests including both RDTs and laboratory instrument-based immunoassays. Expressing test results relative to the candidate material led to a notable improvement in the degree of agreement observed between tests, particularly for the instrument-based tests. The study data also revealed variability in the ability of tests to recognize different SARS-CoV-2 variants. No assessment of commutability of the candidate material to clinical specimens was made as such specimens could not be sourced in the available time-frame. Accelerated thermal degradation data at 5 months indicated that the candidate
material would be stable when stored at −20 °C with the material also exhibiting good in-use stability properties.

Acknowledging that this had been a well-designed and thorough study, the Committee briefly discussed the potential effect of variations in the volume of material absorbed by different swabs. In addition, it was felt that the proposed potency may not be sufficient for use in some test methods. The Committee considered report of the study (WHO/BS/2022.2426) and recommended that candidate material 21/368 be established as the First WHO International Standard for SARS-CoV-2 antigen with an assigned unitage of 5000 IU/ampoule.

8.1.2 Second WHO International Standard for anti-SARS-CoV-2 immunoglobulin; First WHO International Standard for antibodies to SARS-CoV-2 variants of concern; and First WHO International Reference Panel for antibodies to SARS-CoV-2 variants of concern

The First WHO International Standard for anti-SARS-CoV-2 immunoglobulin was established in 2020 for the calibration and harmonization of assays used to evaluate virus neutralizing antibody responses. In addition to its use in neutralization assays (with assigned unitage in IU) this reference standard has also been widely used as a comparator in antibody binding assays that measure the same class of immunoglobulin with the same viral antigen specificity (with assigned unitage in BAU). The availability of such a standard had supported the development of vaccines and other therapeutics, for example by facilitating the definition of protective antibody levels. Unprecedented demand for this international standard had resulted in the entire depletion of its stocks within 8 months of establishment.

Following the emergence of the initial SARS-CoV-2 strain, a number of variants had now evolved that were more transmissible, virulent and/or likely to evade host immunity. These so-called variants of concern (VOC) have necessitated monitoring to assess their impact on the effectiveness of vaccines and therapeutics, as well as to determine their potential to cause re-infection. Of the five VOC identified during the pandemic (Alpha, Beta, Gamma, Delta and Omicron), it was Omicron and its subvariants that now predominated globally, accounting for 98% of viral sequences submitted since February 2022. As the arbitrary unitage assigned to the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin does not equate to a physical measurement, its potency is variant specific. A WHO international reference panel of convalescent plasma or serum from COVID-19 patients infected with a particular VOC would therefore better facilitate evaluation of the impact of VOC on the results of antibody assays. At its meeting in October 2021, the Committee had therefore endorsed proposals to develop both a replacement for the first international standard and an international reference panel of antibodies to SARS-CoV-2 VOC.
An international collaborative study involving 41 laboratories in 15 countries had therefore been conducted to evaluate a number of candidate materials – the first, a pool of plasma (NIBSC code 21/340) had been obtained from convalescent individuals infected in 2020 and was thus similar to the current international standard, while the second, a pool of plasma (NIBSC code 21/338) had been obtained from individuals infected with SARS-CoV-2 (including a VOC) and immunized with the recommended number of COVID-19 vaccine doses. The collaborative study samples also included the candidate reference panel for antibodies to VOC. Three potential panel members had been evaluated – a pool of convalescent plasma (NIBSC code 21/296) obtained from individuals infected with SARS-CoV-2 in 2020, before the emergence of VOC; a pool of plasma (NIBSC code 21/300) obtained from individuals likely to be infected with Alpha; and a pool of sera (NIBSC code 21/312) obtained from recovered patients infected with Delta.

Neutralizing antibody levels in all candidate materials were assessed by live or pseudotyped virus assays or by surrogate neutralization assays. Study participants also returned 107 datasets from antibody binding assays, the majority of which specifically detected IgG. Data from neutralization assays indicated that the potency of candidate material 21/340 was similar to the first international standard, having only slightly more potency against the original SARS-CoV-2 isolate and Alpha, Delta and Omicron variants but less against Beta and Gamma variants. However, not all participants obtained a dose-response curve against Omicron with either the current international standard or candidate material 21/340. In contrast, candidate material 21/388 exhibited more diverse responses, including significantly higher responses against Omicron. Despite not containing convalescent plasma from individuals infected with Omicron, its broad cross-neutralization activity could make it suitable for the evaluation of immune responses to emerging variants. Based on 6 months of stability data the study the characterisation of some of the individual plasma, this pool includes antibodies recognizing alpha, beta and delta VOC. The formulation of both candidates complied WHO recommendations for international standards. Stability data at 6 months indicated that both candidate materials would be stable when stored at −20 °C and would be suitable for shipping at ambient temperature.

All three prospective reference panel members also performed well in all assays, including against VOC with the exception of Omicron (which was not detected in neutralization assays by some laboratories and only weakly by others). Study results indicated that the prospective reference panel would be suitable for facilitating the development and optimization of both neutralization and binding assays. The stability of the reference panel, inferred from previous work, supported its long term storage at −20 °C and distribution at ambient temperature. An accelerated degradation study was under way with the results to be presented to the Committee in March 2023. In addition, convalescent plasma
pools from individuals infected with Gamma and Omicron variants were also undergoing evaluation for potential future inclusion in the panel.

The Committee applauded the considerable work and effort that had been involved in developing these reference materials. Despite some concerns about having such closely related antibody standards for essentially the same purpose, there was a consensus that both candidate material 21/340 and candidate material 21/388 were needed to cover the current situation. The Committee further noted that maintaining continuity with the original international standard would become increasingly difficult as the virus, vaccines and immune responses of donors continued to change. It was also recognised that this also had important implications for the naming of future replacement materials and following extended discussion of the nomenclature conventions to be used for such serological standards, the Committee agreed that the best approach would be to address the issue as each replacement proposal was presented to it.

The Committee also expressed concern that assigning different BAU values to a panel consisting of different VOC would be confusing for users but was assured that only BAU values against the original isolates would be provided. Diagnostic kit manufacturers were not planning to modify their assays for different VOC and such assays were expected to continue to be based on the original antigen. It was further noted that anecdotal evidence from external quality assessment studies suggested that the use of BAU had been remarkably effective at harmonizing antibody binding assay data. The Committee went on to discuss the purpose of panel variants that were no longer in circulation and concluded that the composition of the panel should continue to include sera against historical variants given the prevailing complex situation regarding the development of multivalent vaccines and the uncertainty surrounding the course of virus evolution. The panel would also be useful in maintaining the link with historical data, which may prove important for diagnostic kit manufacturers and regulators assessing the breadth of coverage of new assays. Noting that the panel would include the BA.1 variant of Omicron, the Committee enquired whether it should also include more recent variants such as BA.4 and BA.5. It was concluded that although the panel would inevitably lag behind current epidemiology, novel variants could be flexibly be added to the panel if considered to be epidemiologically important.

The Committee considered the report of the study (WHO/BS/2022.2427) and recommended that candidate material 21/340 be established as the Second WHO International Standard for anti-SARS-CoV-2 immunoglobulin with an assigned unitage of 356 IU/ampoule for the evaluation of neutralizing antibodies to SARS-CoV-2 isolated prior to the emergence of VOC. Recognizing that neither the first nor second international standard could be used for neutralization assays using Omicron, the Committee further recommended that candidate material 21/388 be established as the First WHO International Standard for
antibodies to SARS-CoV-2 variants of concern with an assigned unitage of 4250 IU/ampoule for the quantification of antibodies neutralizing Omicron and other emerging variants. In addition, the Committee recommended that candidate materials 21/296, 21/300 and 21/312 be established as the First WHO International Reference Panel for antibodies to SARS-CoV-2 variants of concern without assigned unitage. The table of geometric mean antibody titres resulting from the collaborative study should be included in the IFU as representative guidance for users.

8.2 Proposed new projects and updates – standards for use in public health emergencies

8.2.1 Proposed Second WHO International Standard for SARS-CoV-2 RNA for NAT-based assays

Diagnostic testing and contact tracing continue to play an important role in the control of SARS-CoV-2 infections. Shortly after the start of the COVID-19 pandemic, an international collaborative study had been rapidly undertaken in order to establish the First WHO International Standard for SARS-CoV-2 RNA for NAT-based assays. Established in December 2020, this reference standard has facilitated the development and assessment of NAT-based assays, including through the improved comparability of assay data, and the determining of limits of detection and assay reliability. Since then, more than 1600 vials have been distributed worldwide, leaving stocks severely depleted. Despite decreased demand in recent months, the need for SARS-CoV-2 molecular diagnostics is expected to continue for the foreseeable future. Currently, there are more than 300 CE-marked IVDs on the market, with 20 having WHO EUL and a further 21 undergoing assessment. Ensuring the continuity of unitage and the availability of the international standard thus remain important in the continued assessment and regulatory review of new and updated molecular diagnostic platforms.

The proposed source material will be a like-for-like heat-inactivated replacement virus based on the Wuhan strain rather than the currently predominant Omicron variant. This is intended to reflect both the importance of maintaining continuity of unitage and the changing epidemiology of infection, which does not support the selection of a more recent strain. An international collaborative study involve 20–30 laboratories, including clinical and public health laboratories, vaccine manufacturers, diagnostic kit manufacturers and research laboratories will be conducted. A broad range of molecular assay methods will be used, including real-time PCR, dPCR, and transcription-mediated amplification and loop-mediated isothermal amplification technologies to encompass a high proportion of commercially available assay methods. Other inactivated SARS-CoV-2 VOC will be included in the study panel along with the SARS-CoV-2 antigen standard discussed during the current meeting (see section 8.1.2 above).
Following a brief discussion of the challenges associated with maintaining continuity of unitage across diverse assay systems, the Committee endorsed the proposal (WHO/BS/2022.2439) to develop a Second WHO International Standard for SARS-CoV-2 RNA for NAT-based assays.

9.1  WHO international reference standards for vaccines and related substances

9.1.1  First WHO international standards for anti-human papillomavirus types 6, 11, 31, 33, 45, 52 and 58 serum

Vaccination against human papillomavirus (HPV) along with infection surveillance, play a crucial role in the WHO Global strategy to accelerate the elimination of cervical cancer as a public health problem – an initiative adopted by the World Health Assembly in 2020. Serological methods are used both to assess the immunogenicity of HPV vaccines and in epidemiological studies to monitor the spread of HPV infection. The need for global assay harmonization has long been recognized by laboratories and organizations working with HPV which otherwise have to rely on their own standardization approaches when harmonizing such assays.

Following the earlier establishment of WHO international standards for anti-HPV types 16 and 18 serum, the Committee endorsed a proposal in 2016 to develop corresponding international standards for HPV6, HPV11, HPV31, HPV33, HPV45, HPV52 and HPV58 serotypes. The availability of such international standards would help to address numerous obstacles to global harmonization in this area by allowing for reporting in a common unitage. Such challenges include the inherent variability of VLP-based assay systems and the resulting variations between sera from vaccinated and infected individuals observed by different laboratories, and the need to harmonize both antibody binding assays and pseudovirus neutralization assays (PVNAs), determine cut-off points and assay sensitivity, and assess specificity. Taken together with the existing two international standards for HPV16 and HPV18, the addition of the above seven international standards would cover all currently licensed vaccine formulations.

An international collaborative study had been conducted involving 11 laboratories in seven countries, including government research, public health, medical research, regulatory organization and HPV manufacturer laboratories. Candidate materials consisting of sera obtained from at least two female donors who had been infected naturally with the HPV type of interest had been sourced from China, Slovenia and Thailand. Following detailed characterization, the candidate materials were assessed for their suitability to serve as WHO international standards, with proposed unitages assigned in IU. Study results indicated that, with the exception of the HPV11 serum, all candidate materials were specific and negative for the other HPV types. The HPV11 serum was
found to also be reactive with HPV6, HPV33, HPV52 and HPV58 in several laboratories, thus confirming previous validation results. This finding was expected as HPV11 shares epitopes with other HPV types and HPV11 antisera are therefore rarely monospecific. Although the HPV11 antibody candidate also experienced a freeze-drying failure resulting in its dehydration instead of lyophilization, post-production validation and study results indicated that it had retained its reactivity.

As noted during the establishment of the two WHO international standards for anti-HPV types 16 and 18 serum, the candidate materials exhibited absolute potencies that were lower compared with sera from vaccinees. Expressing potencies relative to the candidate materials generally harmonized the assays used, with some (HPV11, HPV33 and HPV58) harmonizing assays better than others. Accelerated thermal degradation studies and real-time stability testing supported the long-term storage of the materials at −20 °C and distribution at ambient temperature. It was further proposed that the reference standards be distributed individually as well as part of four-piece (HPV6, HPV11, HPV16 and HPV18) and five-piece (HPV31, HPV33, HPV45, HPV52 and HPV58) panels.

During discussion, the Committee felt that distributing the proposed reference standards as a panel would increase waste and lead to their early replacement. The Committee then sought clarification with regard to the omission of outlier data points when calculating geometric mean titres and assurance was given that such outliers would not normally be omitted without strong justification. Noting that the collaborative study participants were experts in the field, the Committee agreed that the data obtained from all laboratories was important and should be considered, including apparently aberrant data. Further clarification was given that for collaborative studies on establishing a new international standard (as opposed to replacing it) the exclusion of data would have no implications for the arbitrary assignment of unitage and that this was the case for the current establishment studies.

Reflecting on the issues associated with the candidate anti-HPV11 material, the Committee accepted that the predefined requirement for single-serotype specificity was inappropriate in this case due to known cross-reactive epitopes with other HPV types. Despite the unfortunate failure of the lyophilization process for this material, the Committee acknowledged that the collaborative study data supported its use as a reference standard.

The Committee considered the report of the study (WHO/BS/2022.2428) and, mindful of the earlier discussion concerning ongoing issues in the assignment of units to the same material for different assays or activities (see section 2.1.3 above), recommended that the candidate materials be established as First WHO international standards for anti-human papillomavirus types 6, 11, 31, 33, 45, 52 and 58 serum with assigned potencies of:
9.1.2 WHO International Reference Reagent for tetanus antitoxin for use in flocculation test (equine)

Tetanus is caused by a potent neurotoxin produced by the bacterium *Clostridium tetani* and its toxoid is the major component of tetanus vaccines. It is usually administered in paediatric combination vaccines and is also used as a carrier protein in several glycoconjugate vaccines. The amount of toxoid in a sample can be expressed as a “limit of flocculation” (Lf) value determined using a flocculation assay. Toxoid purity, which is an essential quality criterion for vaccine production, is expressed in Lf units/mg of protein nitrogen. The flocculation test is an antibody binding assay that requires a hyperimmune equine tetanus antitoxin as a critical reagent. A lyophilized preparation of hyperimmune equine antitoxin had previously been available from MHRA as a non-WHO reagent but following its widespread use stocks were now completely depleted and replacement material was now needed.

A small international collaborative study had been conducted involving nine laboratories in eight countries to assess the fitness of a candidate material (NIBSC code 21/230) for use in the flocculation test. The candidate material had been prepared from 5 L of donated equine tetanus antitoxin that had been filled and freeze-dried, and which fulfilled the WHO requirements for a reference material. Study results indicated that the candidate material would be suitable for use as a WHO international reference reagent, with an estimated 912 Lf-eq/ampoule (95% CI = 878–948) and an average Kf time of 15 minutes. Good agreement was observed in the results obtained, with intra-laboratory variability ranging from 0% to 6.9% and an inter-laboratory variability of 5.2%. Accelerated thermal degradation studies indicated no temperature-dependent loss in flocculation activity after storage for 3 months at elevated temperatures, indicating that the material was likely to exhibit good long-term stability. Further stability studies would be conducted subject to establishment of the international reference reagent.

The Committee commented that the study appeared to have been straightforward and the results clearly presented. Noting that further stability studies would continue to be performed post establishment, the Committee considered the report of the study (WHO/BS/2022.2431) and recommended

<table>
<thead>
<tr>
<th>HPV type</th>
<th>NIBSC code</th>
<th>IU/ampoule</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>19/298</td>
<td>7</td>
</tr>
<tr>
<td>11</td>
<td>20/174</td>
<td>6</td>
</tr>
<tr>
<td>31</td>
<td>20/176</td>
<td>3</td>
</tr>
<tr>
<td>33</td>
<td>19/290</td>
<td>8</td>
</tr>
<tr>
<td>45</td>
<td>20/178</td>
<td>2</td>
</tr>
<tr>
<td>52</td>
<td>19/296</td>
<td>14</td>
</tr>
<tr>
<td>58</td>
<td>19/300</td>
<td>20</td>
</tr>
</tbody>
</table>
that the candidate material 21/230 be established as the WHO International Reference Reagent for tetanus antitoxin for use in flocculation test (equine) without assigned unitage. The Committee agreed with the proposed approach of advising laboratories performing the assay to pre-calibrate the reference reagent against the Third WHO International Standard for tetanus toxoid for use in flocculation test established in 2019.

9.1.3 Third WHO International Standard for antibodies to rabies virus

Rabies is an important zoonotic infection with substantial public health impact globally. Every year, more than 15 million people receive post-exposure prophylaxis, which includes passive immunization with rabies immunoglobulin and active immunization with vaccine. The evaluation of human rabies immunoglobulin (HRIG) potency is critical in ensuring its consistency and stability. Methods accepted by regulatory authorities for determining HRIG potency measure the neutralization activity of HRIG against rabies challenge virus in cell culture and are based on the rapid fluorescent focus inhibition test (RFFIT) or the fluorescent antibody virus neutralization (FAVN) test, which have replaced the historical mouse neutralization test. The minimum potency requirement for HRIG and levels of rabies serum antibodies determined by other methods are expressed in IU relative to the WHO international standard. Stocks of the Second WHO International Standard for anti-rabies immunoglobulin were now depleted and a proposal to develop a replacement international standard was endorsed by the Committee in 2017.

A candidate material (NIBSC code 19/244) was prepared from an HRIG bulk manufactured according to GMP guidelines, dispensed into ampoules in 0.5 mL aliquots and freeze-dried. Fill variability, mean residual moisture content and mean oxygen content of the head space were all consistent with the requirements for a WHO international standard. An international collaborative study was conducted involving 15 laboratories in seven countries to evaluate the candidate material for its potency and suitability for use. The assay methods used by participants were: RFFIT (n = 10); FAVN (n=3); rabies-specific ELISA (n=3); and rabies pseudovirus-neutralization assay (n = 2). Overall geometric mean potency of the candidate material as evaluated by RFFIT and FAVN was 327.0 IU/mL with a value of 255.4 IU/mL obtained by ELISA, reflecting the different mechanisms of detection.

Intra-laboratory variations in potencies determined by RFFIT and FAVN assays were similar, whether determined relative to in-house standards or to the current WHO international standard, but inter-laboratory variability was reduced when expressed relative to the latter. Higher than expected geometric mean potencies were observed when RFFIT and FAVN data were expressed relative to in-house references, possibly reflecting differences in individual
laboratory procedures for the qualification of in-house standards, but were within 5% of the expected result when expressed relative to the international standard. Applying the Arrhenius formula to the data obtained from thermal degradation studies indicated that the candidate material would be sufficiently stable for long-term storage at −20 °C or below and for shipping at ambient temperature.

The Committee considered the report of the study (WHO/BS/2022.2435) and recommended that candidate material 19/244 be established as the Third WHO International Standard for antibodies to rabies virus with an assigned potency of 164 IU/ampoule for RFFIT and FAVN methods, and 128 IU/ampoule for antibody binding methods. Due to the limited data supporting its use in PVNA no unitage was assigned for this method at the current time but the Committee indicated its willingness to consider a future proposal for this use should sufficient data be produced.

9.1.4 **WHO international reference reagents for potency testing of inactivated poliomyelitis vaccines**

Four years after the declaration of the eradication of wild poliovirus type 2 (WPV2) in 2015, the Global Commission for the Certification of the Eradication of Poliomyelitis concluded that wild poliovirus type 3 (WPV3) had also been eradicated worldwide. Geographically, the detection of wild poliovirus type 1 (WPV1) is now limited to Afghanistan and Pakistan. As a result, the focus of current activities is on preventing all poliovirus transmission in endemic countries and stopping the transmission of circulating vaccine-derived poliovirus (cVDPV). Preventing cVDPV outbreaks will ultimately require the cessation of OPV use and the introduction of IPV worldwide. With the successful eradication of WPV2 and WPV3, higher containment levels for such viruses will be required, and several manufacturers have started to use Sabin poliovirus to produce sIPV as an alternative to wild-type strains to ensure safer vaccine production. With the increased demand for IPV, various new manufacturers are producing or planning to produce sIPV in the near future and licensed sIPV products are already in production. In addition, three licensed sIPVs are WHO prequalified for global use.

The WHO Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (inactivated) provides guidance on the in vitro measurement of IPV D antigen content using a validated ELISA test and suitable reference standards. Although there were currently WHO international standards for the D-antigen content of both conventional IPV (cIPV) and sIPV, the current D-antigen ELISA method also requires antibodies for the capture and detection of IPV that vary depending on the assay method used. In light of the recognized need for further harmonization in this area, the Committee had in 2018 endorsed
a proposal to develop a set of WHO international reference reagents comprising both type-specific and cross-reactive human monoclonal antibodies to improve consistency in the assays used by manufacturers and national control laboratories to determine the D-antigen content of IPV.

An international collaborative study had been conducted involving 15 laboratories in nine countries to develop the required reference reagents. A set of four human monoclonal antibodies had been assessed as candidate materials using blinded samples of both cIPV and sIPV products. Study data showed low intra-assay and inter-assay variability for potency estimates for all samples, and good agreement between laboratories for the potencies determined for all study samples. A higher inter-laboratory variability was observed for sIPV samples when compared to cIPV but this appeared to depend on sample and virus type rather than the reagents or method employed. Real-time data indicated that the candidate materials would be stable at $-20\,^\circ\mathrm{C}$ for more than 12 months, while no loss in potency was observed after 6 weeks at up to $45\,^\circ\mathrm{C}$ during accelerated degradation studies. In addition, the reconstituted materials were stable at $4\,^\circ\mathrm{C}$ for at least 4 weeks and for up to four cycles of freeze-thawing. These results indicated that all four candidate materials would be stable at the recommended storage temperature of $-20\,^\circ\mathrm{C}$, for short-term manipulation in the laboratory and for shipping at ambient temperature.

The Committee considered the report of the study (WHO/BS/2022.2432) and recommended that the human monoclonal type-specific capture antibodies (candidate materials 20/250, 20/252 and 20/254) and the human monoclonal cross-reactive detection antibody (candidate material 20/256) be established as WHO international reference reagents without assigned unitage given their role as capture and detection antibodies.

9.2 Proposed new projects and updates – vaccines and related substances

9.2.1 Proposed Second WHO International Standard for yellow fever vaccine

Yellow fever is a viral haemorrhagic fever endemic to countries in Africa, and Central and South America. It is transmitted from human to human via mosquitoes and can result in high case-fatality rates among non-vaccinated young children and the elderly. Effective live attenuated yellow fever vaccines derived from strain 17D, which are prequalified by WHO, are crucial for the prevention of yellow fever in endemic areas. Although such vaccines are currently produced in eggs, a number of cell-based versions are in development. During potency testing a WHO international standard is used to assign titres in IU and to help validate assays.

In addition to the consistent use of the current international standard by manufacturers already producing yellow fever vaccines, new producers are
now using it to establish vaccine production. As a result, stocks of the First WHO International Standard for yellow fever vaccine, established in 2003, are now critically low and a replacement reference standard was required. It was proposed that an international collaborative study be conducted involving at least eight laboratories, primarily manufacturers and national control laboratories performing in vitro cell-based plaque assay methods. The source material for the prospective standard would be yellow fever vaccine bulk donated by a manufacturer. As there is currently a global shortage of yellow fever vaccines and studies are under way to assess the potential of using fractional doses, obtaining candidate materials may prove challenging. However, two manufacturers had indicated their willingness to provide vaccine bulk, one based in Brazil and the other one in the Russian Federation. It was provisionally intended that the results of the collaborative study would be submitted for consideration by the Committee in October 2024.

Noting the range of 17D variants used to manufacture yellow fever vaccines and the ongoing development of cell-based vaccines, the Committee suggested that the proposed study should be broadened to be as representative as possible, both in terms of 17D variants and manufacturing processes. The Committee endorsed the proposal (WHO/BS/2022.2439) to develop a Second WHO International Standard for yellow fever vaccine.

9.2.2 Update on the WHO collaborative study to investigate the utility of next generation sequencing of virus stocks used in the manufacture of oral poliomyelitis vaccines

The WHO Global Polio Eradication Initiative has been heavily dependent on the use of OPV since its inception. However, the attenuated Sabin poliovirus strains used in the vaccine have long been known to be genetically unstable and can revert to a neurovirulent phenotype during virus passage both in vivo and in vitro. Consequently, it is essential to monitor attenuation during vaccine production. Historically this has been achieved by identifying increases in neurovirulent phenotypes using the monkey neurovirulence test and/or transgenic mice expressing the human poliovirus receptor. Since the late 1980s, attenuation has also been monitored genotypically using the MAPREC test to quantify the reversion of specific mutations in the 5’ untranslated region of the viral genome. Although MAPREC is an effective test that does not require the use of animals, it is technically demanding and expensive, with few laboratories performing the test as a result. However, the advent of HTS technologies has now made it possible to easily and inexpensively evaluate mutations arising during the manufacture of live-attenuated viral vaccines such as OPV.

In 2013, the Committee had endorsed a proposal to conduct an international collaborative study involving several national control laboratories...
and vaccine manufacturers to assess the use of HTS techniques to monitor the molecular consistency of OPV3 during production. Study results demonstrated excellent agreement between laboratories with low intra-laboratory, inter-laboratory and intra-assay variability reported. At the current meeting, the Committee was updated on the results of the second phase of the collaborative study on applying HTS techniques to OPV1 and OPV2 quality control.

Eight study samples for type 1 poliovirus and 7 for type 2 were analysed by two laboratories using their in-house HTS method and the results compared with those obtained from MAPREC testing. For both sample types, intra-laboratory, inter-laboratory and intra-assay variability were very low, indicating good agreement. Although good correlation was observed between MAPREC and HTS measurements, further analysis revealed incomplete concordance, indicating that even though HTS and MAPREC data were proportional, they differed in absolute terms. This finding did not alter the overall conclusion that HTS could be used as an alternative to MAPREC.

Acknowledging the importance of this work and noting that the revised WHO Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated) allowed for the replacement of MAPREC with HTS (see section 3.3.3 above), the Committee sought clarification of the strength of evidence to support such a change for OPV1 and OPV2 quality control. The Committee was assured that HTS could be used for routine lot release using either existing reference materials developed and validated for the MAPREC test or reference materials developed specifically for HTS techniques. In both cases, the acceptance criteria for MAPREC and HTS should be similar. The Committee agreed that the study had effectively been an extension of the similar OPV3 study previously approved by the Committee and that taken together the data showed that MAPREC and HTS were essentially measuring the same mutations. Nevertheless, although not strictly necessary in the short term, a consensus was reached that new reference materials specifically for use in HTS should be developed. Concern was also expressed that as the collaborative study involved only two laboratories, it would not meet WHO requirements. Assurance was given that the approach would be deemed acceptable as this was technically an extension of the previous study conducted for OPV3, which had involved eight laboratories, and taking into account the challenges associated with conducting such studies under current poliovirus containment requirements.

Reflecting on the important impact that HTS technologies were now having in the public health sphere, the Committee noted the study report (WHO/BS/2022.2438) and endorsed the proposed use of HTS methods as an alternative to MAPREC testing for the lot release testing of OPV1 and OPV2, subject to the use of appropriate test formats and to the agreement of the NRA on the analytical processes to be used to establish assay validity and pass/fail criteria. Care should also be taken to align the revised WHO Recommendations
(see section 3.3.3 above) with this approach. The Committee also endorsed the proposal to continue the project and thereby develop an approach for sequencing the whole viral genome as a lot release test for all three types of OPV. To this end, the Committee suggested that WHO should consider supporting the development of a database of mutations identified by different manufacturers, as well as algorithms to aid the interpretation of results and establish the range of acceptable variation.
WHO Recommendations, Guidelines and other documents related to the manufacture, quality control and evaluation of biological products

WHO Recommendations, Guidelines and other documents are intended to provide guidance to those responsible for the development and manufacture of biological products as well as to others who may have to decide upon appropriate methods of assay and control to ensure that such products are safe, reliable and potent. WHO Recommendations (previously called Requirements) and Guidelines are scientific and advisory in nature but may be adopted by an NRA as national requirements or used as the basis of such requirements.

Recommendations and guidance on biological products are formulated by international groups of experts and published in the WHO Technical Report Series as listed below. A historical list of Requirements and other sets of Recommendations is available on request from the World Health Organization, 20 avenue Appia, 1211 Geneva 27, Switzerland.

Reports of the WHO Expert Committee on Biological Standardization published in the WHO Technical Report Series can be purchased from:

WHO Press
World Health Organization
20 avenue Appia, 1211 Geneva 27
Switzerland
Email: bookorders@who.int
Website: www.who.int/bookorders

Individual Recommendations and Guidelines and other documents may be obtained free of charge as offprints by writing to:

Technical Standards and Specifications unit
Department of Health Product Policy and Standards
Access to Medicines and Health Products
World Health Organization
20 avenue Appia, 1211 Geneva 27
Switzerland

---

7 Abbreviated in the following pages to “TRS”. 
<table>
<thead>
<tr>
<th>Recommendations, Guidelines and other documents</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal cells, use of, as in vitro substrates for the production of biologicals</td>
<td>Revised 2010, TRS 978 (2013)</td>
</tr>
<tr>
<td>BCG vaccines (dried)</td>
<td>Revised 2011, TRS 979 (2013)</td>
</tr>
<tr>
<td>Biological products: good manufacturing practices</td>
<td>Revised 2015, TRS 999 (2016)</td>
</tr>
<tr>
<td>Biological standardization and control: a scientific review commissioned by the UK National Biological Standards Board (1997)</td>
<td>Unpublished document WHO/BLG/97.1</td>
</tr>
<tr>
<td>Biosimilars, evaluation of</td>
<td>Revised 2022, TRS 1043 (2022)</td>
</tr>
<tr>
<td>Biotherapeutic products, changes to approved biotherapeutic products: procedures and data requirements</td>
<td>Adopted 2017, TRS 1011 (2018)</td>
</tr>
<tr>
<td>Biotherapeutic protein products prepared by recombinant DNA technology</td>
<td>Revised 2013, TRS 987 (2014); Addendum 2015, TRS 999 (2016)</td>
</tr>
<tr>
<td>Diphtheria, tetanus, pertussis (whole cell), and combined (DTwP) vaccines</td>
<td>Revised 2012, TRS 980 (2014)</td>
</tr>
<tr>
<td>Recommendations, Guidelines and other documents</td>
<td>Reference</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Diphtheria vaccines (adsorbed)</td>
<td>Revised 2012, TRS 980 (2014)</td>
</tr>
<tr>
<td>DNA vaccines, plasmid</td>
<td>Revised 2020, TRS 1028 (2021)</td>
</tr>
<tr>
<td>Enterovirus 71 vaccines (inactivated)</td>
<td>Adopted 2020, TRS 1030 (2021)</td>
</tr>
<tr>
<td>Haemorrhagic fever with renal syndrome (HFRS) vaccines (inactivated)</td>
<td>Adopted 1993, TRS 848 (1994)</td>
</tr>
<tr>
<td>Hepatitis B vaccines prepared from plasma</td>
<td>Revised 1994, TRS 858 (1996)</td>
</tr>
<tr>
<td>Hepatitis B vaccines (recombinant)</td>
<td>Revised 2010, TRS 978 (2013)</td>
</tr>
<tr>
<td>Human immunodeficiency virus rapid diagnostic tests for professional use and/or self-testing Technical Specifications Series for WHO Prequalification – Diagnostic Assessment</td>
<td>Adopted 2017, TRS 1011 (2018)</td>
</tr>
<tr>
<td>Human interferons prepared from lymphoblastoid cells</td>
<td>Adopted 1988, TRS 786 (1989)</td>
</tr>
<tr>
<td>Influenza vaccines (inactivated)</td>
<td>Revised 2003, TRS 927 (2005)</td>
</tr>
<tr>
<td>Influenza vaccines (live)</td>
<td>Revised 2009, TRS 977 (2013)</td>
</tr>
<tr>
<td>Influenza vaccines, human, pandemic: regulatory preparedness</td>
<td>Adopted 2007, TRS 963 (2011)</td>
</tr>
<tr>
<td>In vitro diagnostics (WHO-prequalified), collaborative procedure between WHO and NRAs for assessment and accelerated national registration</td>
<td>Adopted 2020, TRS 1030 (2021)</td>
</tr>
<tr>
<td>Recommendations, Guidelines and other documents</td>
<td>Reference</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Japanese encephalitis vaccines (inactivated) for human use</td>
<td>Revised 2007, TRS 963 (2011)</td>
</tr>
<tr>
<td>Japanese encephalitis vaccines (live, attenuated) for human use</td>
<td>Revised 2012, TRS 980 (2014)</td>
</tr>
<tr>
<td>Malaria vaccines (recombinant)</td>
<td>Adopted 2012, TRS 980 (2014)</td>
</tr>
<tr>
<td>Medical devices including in vitro diagnostic medical devices, WHO Global Model Regulatory Framework for, WHO Medical device technical series</td>
<td>Revised 2022, TRS 1045 (2023)</td>
</tr>
<tr>
<td>Meningococcal A conjugate vaccines</td>
<td>Adopted 2006, TRS 962 (2011)</td>
</tr>
<tr>
<td>Meningococcal C conjugate vaccines</td>
<td>Adopted 2001, TRS 924 (2004); Addendum (revised) 2007, TRS 963 (2011)</td>
</tr>
<tr>
<td>Monoclonal antibodies, production and quality control</td>
<td>Revised 2022, TRS 1043 (2022)</td>
</tr>
<tr>
<td>Monoclonal antibodies as similar biotherapeutic products</td>
<td>Adopted 2016, TRS 1004 (2017)</td>
</tr>
<tr>
<td>Papillomavirus vaccines (human, recombinant, virus-like particle)</td>
<td>Revised 2015, TRS 999 (2016)</td>
</tr>
<tr>
<td>Pertussis vaccines (acellular)</td>
<td>Revised 2011, TRS 979 (2013)</td>
</tr>
<tr>
<td>Recommendations, Guidelines and other documents</td>
<td>Reference</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Pneumococcal conjugate vaccines</td>
<td>Revised 2009, TRS 977 (2013)</td>
</tr>
<tr>
<td>Poliomyelitis vaccines (inactivated)</td>
<td>Revised 2014, TRS 993 (2015); Amendment 2019, TRS 1024 (2020)</td>
</tr>
<tr>
<td>Poliomyelitis vaccines (oral)</td>
<td>Revised 2022, TRS 1045 (2023)</td>
</tr>
<tr>
<td>Poliomyelitis vaccines: safe production and quality control</td>
<td>Revised 2018, TRS 1016 (2019); Amendment 2020, TRS 1028 (2021)</td>
</tr>
<tr>
<td>Reference materials, secondary: for antibody testing</td>
<td>Adopted 2022, TRS 1043 (2022)</td>
</tr>
<tr>
<td>Regulation and licensing of biological products in countries with newly developing regulatory authorities</td>
<td>Adopted 1994, TRS 858 (1995)</td>
</tr>
<tr>
<td>Respiratory syncytial virus vaccines</td>
<td>Adopted 2019, TRS 1024 (2020)</td>
</tr>
<tr>
<td>RNA vaccines, messenger, for prevention of infectious diseases</td>
<td>Adopted 2021, TRS 1039 (2022)</td>
</tr>
<tr>
<td>Snake antivenom immunoglobulins</td>
<td>Revised 2016, TRS 1004 (2017)</td>
</tr>
<tr>
<td>Synthetic peptide vaccines</td>
<td>Adopted 1997, TRS 889 (1999)</td>
</tr>
<tr>
<td>Tetanus vaccines (adsorbed)</td>
<td>Revised 2012, TRS 980 (2014)</td>
</tr>
<tr>
<td>Recommendations, Guidelines and other documents</td>
<td>Reference</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Thromboplastins and plasma used to control oral anticoagulant therapy</td>
<td>Revised 2011, TRS 979 (2013)</td>
</tr>
<tr>
<td>Transmissible spongiform encephalopathies in relation to biological and pharmaceutical products&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Revised 2005, WHO (2006)</td>
</tr>
<tr>
<td>Tuberculins</td>
<td>Revised 1985, TRS 745 (1987)</td>
</tr>
<tr>
<td>Typhoid vaccines, conjugated</td>
<td>Revised 2020, TRS 1030 (2021)</td>
</tr>
<tr>
<td>Vaccines, changes to approved vaccines: procedures and data requirements</td>
<td>Adopted 2014, TRS 993 (2015)</td>
</tr>
<tr>
<td>Vaccines, lot release</td>
<td>Adopted 2010, TRS 978 (2013)</td>
</tr>
<tr>
<td>Vaccines, nonclinical evaluation</td>
<td>Adopted 2003, TRS 927 (2005)</td>
</tr>
<tr>
<td>Vaccines, nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines</td>
<td>Adopted 2013, TRS 987 (2014)</td>
</tr>
<tr>
<td>Vaccines, prequalification procedure</td>
<td>Adopted 2010, TRS 978 (2013)</td>
</tr>
<tr>
<td>Vaccines, stability evaluation</td>
<td>Adopted 2006, TRS 962 (2011)</td>
</tr>
<tr>
<td>Vaccines, stability evaluation for use under extended controlled temperature conditions</td>
<td>Adopted 2015, TRS 999 (2016)</td>
</tr>
<tr>
<td>Varicella vaccines (live)</td>
<td>Revised 1993, TRS 848 (1994)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations, Guidelines and other documents</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow fever vaccines, laboratories approved by WHO for the production of</td>
<td>Revised 1995, TRS 872 (1998)</td>
</tr>
<tr>
<td>Yellow fever virus, production and testing of WHO primary seed lot 213-77 and reference batch 168-736</td>
<td>Adopted 1985, TRS 745 (1987)</td>
</tr>
</tbody>
</table>
Annex 2

Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated)


Introduction 69
Purpose and scope 71
Terminology 72
General considerations 74
International reference materials 83
Part A. Manufacturing recommendations 84
  A.1 Definitions 84
  A.2 General manufacturing recommendations 84
  A.3 Control of source materials 84
  A.4 Control of vaccine production 91
  A.5 Filling and containers 101
  A.6 Control tests on the final lot 101
  A.7 Records 104
  A.8 Retained samples 104
  A.9 Labelling 104
  A.10 Distribution and shipping 105
  A.11 Stability testing, storage and expiry date 105
Part B. Nonclinical evaluation of poliomyelitis vaccines (oral, live, attenuated) 106
  B.1 Characterization of a new Sabin virus sub-master seed 107
  B.2 Characterization of virus seeds for the production of nOPV 107
  B.3 Evaluation of immunogenicity of nOPV in suitable models 107
Part C. Clinical evaluation of poliomyelitis vaccines (oral, live, attenuated) 108
  C.1 General considerations 109
  C.2 Immunogenicity and safety studies 109
  C.3 Post-marketing studies and surveillance 112
Part D. Recommendations for NRAs 113
  D.1 General recommendations 113
  D.2 Official release and certification 114
Recommendations published by the World Health Organization (WHO) are intended to be scientific and advisory in nature. Each of the following sections constitutes recommendations for national regulatory authorities (NRAs) and for manufacturers of biological products. If an NRA so desires, these WHO Recommendations may be adopted as definitive national requirements, or modifications may be justified and made by the NRA. It is recommended that modifications to these Recommendations be made only on condition that such modifications ensure that the product is at least as safe and efficacious as that prepared in accordance with the recommendations set out below. The parts of each section printed in small type are comments or examples intended to provide additional guidance to manufacturers and NRAs.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5’ UTR</td>
<td>5’ untranslated region</td>
</tr>
<tr>
<td>bOPV</td>
<td>bivalent oral poliomyelitis vaccine</td>
</tr>
<tr>
<td>CBER</td>
<td>FDA Centre for Biologics Evaluation and Research</td>
</tr>
<tr>
<td>CCID&lt;sub&gt;50&lt;/sub&gt;</td>
<td>cell culture infectious dose 50%</td>
</tr>
<tr>
<td>cVDPV</td>
<td>circulating vaccine-derived poliovirus</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization</td>
</tr>
<tr>
<td>EUL</td>
<td>WHO emergency use listing</td>
</tr>
<tr>
<td>GAPIII</td>
<td>WHO Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use</td>
</tr>
<tr>
<td>GAPIV</td>
<td>WHO Global Action Plan for Poliovirus Containment</td>
</tr>
<tr>
<td>GPEI</td>
<td>Global Polio Eradication Initiative</td>
</tr>
<tr>
<td>HTS</td>
<td>high-throughput sequencing</td>
</tr>
<tr>
<td>IPV</td>
<td>inactivated poliomyelitis vaccine</td>
</tr>
<tr>
<td>MAPREC</td>
<td>mutant analysis by polymerase chain reaction and restriction enzyme cleavage</td>
</tr>
<tr>
<td>MCB</td>
<td>master cell bank</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
</tr>
<tr>
<td>MNVT</td>
<td>monkey neurovirulence test</td>
</tr>
<tr>
<td>mOPV</td>
<td>monovalent oral poliomyelitis vaccine</td>
</tr>
<tr>
<td>NAT</td>
<td>nucleic acid amplification technique</td>
</tr>
<tr>
<td>NCL</td>
<td>national control laboratory</td>
</tr>
<tr>
<td>nOPV</td>
<td>novel oral poliomyelitis vaccine</td>
</tr>
<tr>
<td>NRA</td>
<td>national regulatory authority</td>
</tr>
<tr>
<td>NVT</td>
<td>neurovirulence test</td>
</tr>
<tr>
<td>OPV</td>
<td>oral poliomyelitis vaccine</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>rcDNA</td>
<td>residual cellular DNA</td>
</tr>
<tr>
<td>rct40</td>
<td>reproductive capacity at elevated temperature</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>RSO</td>
<td>RNA-plaque-purified Sabin Original</td>
</tr>
<tr>
<td>SAGE</td>
<td>WHO Strategic Advisory Group of Experts on Immunization</td>
</tr>
<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
</tr>
<tr>
<td>SO</td>
<td>Sabin Original</td>
</tr>
<tr>
<td>SOM</td>
<td>Sabin Original Merck</td>
</tr>
<tr>
<td>SOP</td>
<td>standard operating procedure(s)</td>
</tr>
<tr>
<td>SV40</td>
<td>simian virus 40</td>
</tr>
<tr>
<td>TgmNVT</td>
<td>transgenic mouse neurovirulence test</td>
</tr>
<tr>
<td>TgPVR21 mice</td>
<td>transgenic mice expressing the human poliovirus receptor</td>
</tr>
<tr>
<td>tOPV</td>
<td>trivalent oral poliomyelitis vaccine</td>
</tr>
<tr>
<td>VAPP</td>
<td>vaccine-associated paralytic poliomyelitis</td>
</tr>
<tr>
<td>WCB</td>
<td>working cell bank</td>
</tr>
<tr>
<td>WPV</td>
<td>wild poliovirus</td>
</tr>
</tbody>
</table>
Introduction

WHO Requirements for oral poliomyelitis vaccine (OPV) were first formulated in 1962 (1) and then revised in 1966 (2) and 1972 (3) when an appendix describing the production of OPV in human diploid cells was added. The Requirements were further updated in 1982 (4) to reflect an accumulation of data, particularly on the performance and evaluation of the monkey neurovirulence test (MNVT) and tests on the karyology of human diploid cells. The Requirements were then updated in full in 1989 (5) to take account of the WHO Requirements for continuous cell lines used for biologicals production, which had been adopted in 1985 (6) – with a WHO Study Group concluding that, in principle, such cell lines were acceptable for use as substrates for the production of biologicals (7). An addendum was subsequently adopted (8) that: (a) introduced changes in tests for freedom from detectable DNA sequences of simian virus 40 (SV40); (b) introduced the mutant analysis by polymerase chain reaction and restriction enzyme cleavage (MAPREC) assay as an optional additional in vitro test for poliovirus type 3; (c) increased levels of laboratory containment for wild polioviruses (WPVs); and (d) provided guidance on additional antibody screening tests (for foamy viruses) for animals from closed primate colonies used as a source of primary monkey kidney cells.

The Requirements were subsequently revised in full in 1999 (9) when they became the WHO Recommendations for the production and control of poliomyelitis vaccine (oral). The changes introduced included the use of transgenic mice expressing the human poliovirus receptor (TgPVR21 mice) (10) as an alternative to the MNVT for type 3 virus, and the introduction of the MAPREC assay as the in vitro test of preference for the evaluation of filtered bulk suspensions of poliovirus type 3 (11). The previously mandated reproductive capacity at elevated temperature (rct40) test then became an optional additional test if MAPREC was performed. In 2000, following the completion of studies of poliovirus types 1 and 2 in TgPVR21 mice, an addendum to the Recommendations was adopted (12) that included the transgenic mouse neurovirulence test (TgmNVT) as an alternative to the MNVT for all three poliovirus serotypes.

In 2012, the fully revised WHO Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated) were adopted. The revised Recommendations provided updated information on the origins of different virus strains used for OPV production, as well as consideration of new monovalent OPV (mOPV) and bivalent OPV (bOPV) vaccine formulations (13). Updated sections were also provided on international standards and other reference materials, general manufacturing recommendations and control tests, and on WHO standard operating procedures (SOP) for the TgmNVT and MAPREC in light of technical developments. Other changes included the provision of new sections on the nonclinical and clinical evaluation of OPV,
updating of terminology and the introduction of the “virus sub-master seed lot” concept applicable only to the virus master seed supplied by WHO. Updated guidance was also given on the use of neurovirulence testing (MNVT and TgmNVT) and on the MAPREC assay, which was extended to include all three types of virus seeds and vaccine bulks. A rationale was also provided to guide the choice of monkey or mouse neurovirulence testing.

Since then, significant progress has been made towards global polio eradication, and important advances made in scientific knowledge, novel laboratory techniques (including the use of high-throughput sequencing (HTS), also known as next generation sequencing, massively parallel, or deep sequencing), and the development of new non-pathogenic strains of polioviruses for use in quality control tests. The global eradication of WPVs of serotypes 2 and 3 was declared by WHO in 2015 and 2019, respectively. In early 2016, following the declaration of WPV serotype 2 eradication, the global use of trivalent OPV (tOPV) for routine immunization was replaced by the exclusive use of bOPV containing only serotypes 1 and 3. Therefore, the routine use of tOPV was discontinued, with bOPV now being used for routine and supplemental immunization. mOPV against type 2 (mOPV2) is used to control outbreaks of type 2 circulating vaccine-derived poliovirus (cVDPV2). In addition, tOPV was approved by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) for use in the control of cVDPV2 outbreaks occurring alongside WPV1 circulation. Rationally designed and more genetically stable strains of Sabin 2 poliovirus were developed to minimize reversion of the vaccine strain to virulence and have been used to manufacture novel OPV2 (nOPV2). At the end of 2020, nOPV2 was introduced for cVDPV2 outbreak control under the WHO emergency use listing (EUL) procedure (14).

Since the 2012 revision of the WHO Recommendations, new WHO guidance documents have also been issued. The WHO Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use (GAPIII) was adopted in 2014 (15), with a subsequently revised 4th edition (GAPIV) produced in 2022 (16). The resulting tightened biosafety and biosecurity requirements for handling live polioviruses led to the adoption of the revised WHO Guidelines for the safe production and quality control of poliomyelitis vaccines in 2018 (17), and its subsequent amendment in 2020 (18). Also in 2020, the WHO Expert Committee on Biological Standardization recommended that the 2012 OPV Recommendations should be revised. In response, WHO convened a drafting group composed of national regulators to prepare the revised document. A virtual informal consultation was held by WHO on 15–17 November 2021 attended by experts and representatives from academia, national regulatory authorities (NRAs)/national control laboratories (NCLs), industry, and other international organizations and institutions involved in the research, manufacture,
authorization and testing/release of OPV to discuss and reach consensus on the
issues to be addressed in the revision process (19).

The major issues addressed in the revised Recommendations include:

- the use of HTS in quality control of OPV as an alternative to the
  MAPREC assay as a preferred in vitro test;
- analysis of whole genome mutational profiles generated by HTS as a
  possible future replacement of the MNVT and TgmNVT for routine
  lot release once manufacturing consistency has been established –
  practical experience in these areas is currently limited and further
  guidance will be provided in due course;
- removal of the rct40 test due to its insufficient sensitivity and
  requirement for WPVs as control strains which complicates GAPIV
  compliance;
- consideration of the design, manufacture and quality control of
  nOPV strains;
- use of new non-pathogenic strains for the measurement of
  neutralizing antibodies to polioviruses;
- updates on international reference materials relevant to OPV
  manufacture and control, and inclusion of a new appendix on such
  materials;
- updating of terminology;
- introduction of the “virus sub-master seed” concept for nOPV
  strains in addition to Sabin OPV; and
- the clinical evaluation of new and safer OPV strains that may be
  developed.

Additional changes have also been made to refer to, and align the current
document with, other WHO recommendations published since its previous
revision.

**Purpose and scope**

These WHO Recommendations provide guidance to NRAs and manufacturers
on the manufacturing processes, quality control, and nonclinical and clinical
evaluation needed to assure the quality, safety and efficacy of live attenuated
poliomyelitis vaccines (oral).

The scope of these Recommendations encompasses live attenuated
poliomyelitis vaccines (oral) derived from the original Sabin strains – some by
simple passage and others by more complex routes, including plaque purification.
The document is intended to apply to all OPV products prepared from Sabin poliovirus strains and their derivatives.

The document also includes consideration of the issues raised in the manufacture and control of nOPV made from rationally designed strains created by targeted genetic manipulation of Sabin viruses, and by the introduction of HTS as a quality control method for both nOPV and Sabin OPV.

In the current document, “OPV” refers to oral poliomyelitis vaccines made from any attenuated poliovirus – both the original Sabin strain and novel, genetically modified strains. In some cases, the terms “Sabin OPV” and “nOPV” are used to distinguish between classical OPV and novel OPV.

These WHO Recommendations should be read in conjunction with other relevant WHO guidelines and guidance documents, such as those on nonclinical (20) and clinical (21) evaluation of vaccines, good manufacturing practices for biological products (22), characterization of cell banks (23), lot release (24) and the safe production and quality control of poliomyelitis vaccines (17, 18).

Terminology

The definitions given below apply to the terms as used in these WHO Recommendations. These terms may have different meanings in other contexts.

Adventitious agents: contaminating microorganisms of the cell substrates, or source materials used in their culture, that may include bacteria, fungi, mycoplasmas and endogenous and exogenous viruses that have been unintentionally introduced.

Cell culture infectious dose 50% (CCID_{50}): the quantity of a virus suspension that will infect 50% of cell cultures.

Cell seed: a quantity of vials containing well-characterized cells derived from a single tissue or cell of human or animal origin stored frozen in liquid nitrogen in aliquots of uniform composition, one or more of which will be used for the production of a master cell bank (MCB).

Comparator vaccine: an approved vaccine with established efficacy or with traceability to a vaccine with established efficacy that is tested in parallel with an experimental vaccine and serves as an active control in nonclinical or clinical testing.

Final bulk: the finished vaccine preparation from which the final containers are filled. The final bulk may be prepared from one or more monovalent bulks and may contain more than one virus type.

Final lot: a collection of sealed final containers of finished vaccine that is homogeneous with respect to the risk of contamination during the filling process. All the final containers must therefore have been filled from a single vessel of final bulk in one working session.
High-throughput sequencing (HTS): a next generation sequencing (NGS) technology based on sequencing of individual nucleic acid molecules that allows each nucleotide to be sequenced multiple times (massively parallel or deep sequencing), thereby enabling the detection and quantitation of sequence heterogeneities including single nucleotide polymorphisms (SNPs).

Master cell bank (MCB): a quantity of well-characterized cells of human or animal origin derived from the cell seed and frozen in aliquots of uniform composition at −70 °C or below. The MCB is itself an aliquot of a single pool of cells that has been dispensed into multiple containers and stored under defined conditions (such as the vapour or liquid phase of liquid nitrogen). The MCB is used to derive all working cell banks. The testing performed on a replacement MCB – derived from the same cell clone or from an existing master or working cell bank (WCB) – is the same as that for the initial MCB unless a justified exception is made.

Monovalent bulk: a pool of a number of single harvests of the same virus type processed at the same time.

Novel OPV (nOPV): any OPV manufactured using rationally designed genetically modified derivatives of the live attenuated Sabin vaccine strain. nOPV strains have enhanced genetic stability and lower risk of reversion to neurovirulence compared to the original Sabin strain.

Production cell culture: a cell culture derived from one or more ampoules of the WCB or primary tissue used for the production of vaccines.

RSO (re-derived Sabin Original): RNA-plaque-purified Sabin Original (25). All subsequent passages are designated by an additional number – for example, RSO+1 (master seed) is one passage on from RSO. It is distributed to vaccine manufacturers that create their own virus master seed lot, virus sub-master seed lot and virus working seed lot for the manufacture of monovalent bulks of OPV3.

Sabin strain: any preparation of an attenuated poliovirus of type 1, 2 or 3 derived by a limited number of passages from stocks developed by Dr Albert Sabin (26) and which retain attenuated properties as measured by biological and molecular markers.

Single harvest: a quantity of virus suspension of one virus type harvested from cell cultures derived from the same WCB and prepared during a single production run.

Sabin Original (SO): as described by Sabin and Boulger (26). All subsequent passages are designated by an additional number – for example, SO+1 is one passage on from SO.

Virus master seed lot: a quantity of virus suspension that has been processed at the same time in a single production run to assure a uniform composition, and which has been characterized to the extent necessary to
support development of the virus working seed lot or a virus sub-master seed lot (if applicable).

**Virus sub-master seed lot**: a quantity of virus suspension produced by a single passage from the virus master seed and made at a multiplicity of infection that ensures the development of cytopathic effect within an appropriate timeframe, and which has been processed at the same time in a single production run to assure a uniform composition. Sub-master seed lots should be made by the manufacturer when the supply of a well-characterized master seed of Sabin OPV supplied by WHO is insufficient to meet production needs. They may also be produced from qualified nOPV master seeds if necessary. The virus sub-master seed lot should be characterized as extensively as the virus master seed lot to support the development of the virus working seed lot. The characterized virus sub-master seed lot is used for the preparation of virus working seed lots (see section A.3.2.2 and Part B).

**Virus working seed lot**: a quantity of virus suspension of uniform composition, fully characterized, derived by only one passage from a master or sub-master virus seed lot and approved by the NRA for the manufacturing of vaccine, and made at a multiplicity of infection that ensures the development at cytopathic effect within an appropriate timeframe (for example, 3 days).

**Working cell bank (WCB)**: a quantity of cells of uniform composition derived from one or more ampoules of the MCB at a finite passage level, stored frozen at −70 °C or below in aliquots, one or more of which will be used for vaccine production. All containers are treated identically and once removed from storage are not returned to stock.

**General considerations**

Poliomyelitis is an acute communicable disease of humans caused by three distinct poliovirus serotypes (types 1, 2 and 3) that can be distinguished through neutralization with type-specific antibodies (27). Poliovirus is a species C human enterovirus of the Picornaviridae family and consists of a single-stranded, positive-sense RNA genome and a protein capsid.

Where sanitation is poor, polioviruses are believed to spread mainly by faecal-to-oral transmission, with the oral-to-oral mode of transmission probably dominating in areas with a higher standard of sanitation. Mixed patterns of transmission are likely to occur in most settings. In the pre-vaccine era, around 1 in every 200 susceptible individuals infected by polioviruses developed paralytic poliomyelitis, while the rest were asymptomatic or had mild symptoms (27).

Progress in polio control (and, since 1988, in polio eradication) has been mainly due to the widespread use of vaccines. An inactivated poliomyelitis vaccine (IPV Salk vaccine) was licensed in 1955. The use of live, attenuated OPV (Sabin vaccine) for mass immunizations started in the Soviet Union and a few
other countries in 1959. In the United States and some European countries, an mOPV was licensed in 1961 followed by a tOPV in 1963. The strains of poliovirus used in the production of Sabin OPV were shown to be both immunogenic and highly attenuated when administered orally to susceptible children and adults. Most countries that initially introduced vaccination with IPV later changed to OPV because of its ease of administration, suitability for mass vaccination campaigns, induction of superior intestinal mucosal immunity and lower production costs. In 1974, OPV was recommended as part of the Expanded Programme on Immunization (EPI), and was again the vaccine of choice in 1988 when the World Health Assembly resolved to eradicate polio globally by the year 2000. The last cases of poliomyelitis caused by WPV type 2 (WPV2) and 3 (WPV3) were reported in October 1999 in India and in November 2012 in Nigeria, respectively. Subsequently, the global eradication of WPV2 and WPV3 was certified on 20 September 2015 and 24 October 2019, respectively (27). By the end of 2021, WPV1 remained endemic in only two countries – Afghanistan and Pakistan.

Although OPV is safe, adverse events may occur on rare occasions (27). Vaccine-associated paralytic poliomyelitis (VAPP) is the most important of these rare adverse events and is clinically indistinguishable from poliomyelitis caused by WPV. The identification of VAPP requires laboratory analysis of the virus isolated from the case. VAPP incidence has been estimated at 2–4 cases per million annual birth cohort in countries using OPV (27). Sabin viruses can spread in populations where OPV coverage is low. In such situations, Sabin viruses can acquire the neurovirulence and transmissibility characteristics of WPV, thus becoming cVDPV that can cause outbreaks of the disease (28), presenting a significant challenge to the global eradication campaign. cVDPV2 is the predominant type, and its continued circulation is fuelled by inadequate population immunity. To prevent gaps in population immunity, the switch from tOPV to bOPV (containing only type 1 and type 3 vaccine viruses) was supposed to be accompanied by the introduction of supplemental immunization with trivalent IPV. However, the shortage of IPV in some countries led to a decline in population immunity to type 2 poliovirus and to an increase in cVDPV2 cases from 2 in 2016 to over 1000 in 2020. Outbreaks of cVDPV2 have been controlled through the targeted use of mOPV2, but where the vaccination campaigns have been poor due to difficulties in delivery, they have triggered the emergence of new cVDPV2 outbreaks. To a lesser extent, outbreaks caused by type 1 and 3 cVDPVs have also occurred, and have continued to occur in recent years.

cVDPVs will continue to emerge as long as classical Sabin OPV is used and gaps in population immunity exist. To overcome this problem, in 2011 an international consortium of scientists sponsored by the Bill & Melinda Gates Foundation set out to develop novel vaccine strains with a lower risk of losing their attenuated phenotype and evolving into neurovirulent cVDPVs. One such
virus has now been used to produce an nOPV2 which has been granted EUL by WHO for use in cVDPV2 outbreaks (29–32). Additional strains may be developed in the future, including similar genetically stabilized type 1 and type 3 strains. The design of such novel strains is based on an understanding of the molecular biology of polioviruses and vaccines gained over the years. The attenuation of the Sabin strains is associated in part with a highly base-paired hairpin structure (domain V) in the 5′ untranslated region (5′ UTR) of the virus, which is involved in the initiation of protein synthesis. The three Sabin strains have less thermally stable domain V structures compared to the respective wild strains as a result of the introduction of a single base change in this section of the RNA – which is different for each serotype, but which changes the strength of a base pair. As it is a single base change, all three serotypes can readily revert following a single mutational event to the wild-type sequence at this position, as has been observed in vaccine recipients. Viruses have therefore been designed in which it is harder for the hairpin structure of domain V to become stronger by mutation. This was achieved by replacing stronger GC pairs and weaker GU pairs with intermediately strong AU pairs so that the overall thermostability of the hairpin, and therefore virus neurovirulence, remain unchanged. However, this makes the attenuated phenotype more stable because in this redesigned structure two simultaneous mutations at any given position would be required to revert to the wild-type base pair strength. The nOPV strains should therefore be at least as attenuated as the Sabin strains and genetically more stable. This was demonstrated to be the case in vitro, in animal models and in human trials. Modifications were also introduced into the viral polymerase to increase virus genetic stability by reducing mutation and recombination rates. In addition, an essential cis-acting replicative element was moved from the centre of the genome to the 5′ UTR to minimize the risk of the genetically modified domain V region being removed by recombination.

The key to nOPV safety lies in the low level of reversion at key known sites. Consistency has therefore been monitored by molecular means rather than animal tests – though animal tests are retained as a final check. Because nOPV strains have different properties to the classical Sabin strains with respect to optimal growth conditions, the production and quality control of vaccines made from them may differ from those made using classical Sabin strains. Such differences could include growth and titration properties, optimal temperature of growth, dose required, thermal stability and other parameters. The nucleotide sequence of the nOPV2 strain is available in GenBank9 (accession number MZ245455) and a graphical representation of its structure is provided below in Fig. 3 of Appendix 1. Similar nOPV1 and nOPV3 strains are currently in early clinical development and may be used in future trivalent formulations. Such

novel strains are of great importance to the polio eradication programme and are therefore considered in these revised WHO Recommendations.

Trivalent formulations of conventional (Sabin) OPV were created in the early 1960s to ensure that the immune response against all three poliovirus serotypes was adequate. However, subsequent studies demonstrated that the Sabin 2 virus had higher fitness and interfered with the immunogenicity of serotypes 1 and 3, leading to lower seroconversion (33). In 2008, a clinical trial to evaluate the immunogenicity of alternative OPV formulations (mOPV1, mOPV3 and bOPV) compared to tOPV was conducted in India by WHO. Seroconversion rates to poliovirus type 1 and type 3 following immunization with bOPV were significantly higher than those induced by tOPV, and were not lower than those induced by immunization with either mOPV1 or mOPV3 alone (34). The introduction and widespread use of mOPV1 and mOPV3 in supplementary immunization activities in 2005 led to substantial reductions in cases caused by the respective serotypes. This resulted in the cessation of WPV1 circulation in India and to WPV3 eradication worldwide in 2019. However, the continued circulation of WPV1 in the two remaining polio-endemic countries still requires huge quantities of bOPV to be given in routine and mass campaigns conducted in around 140 countries throughout the world.

In addition to bOPV, which is used in most countries for routine or supplementary vaccination, mOPVs of all three serotypes are used by the Global Polio Eradication Initiative (GPEI)10 and have been licensed for use in endemic countries and for outbreak control in situations where one or two types can re-emerge. In 2020, SAGE recommended that tOPV be made available to countries for cVDPV2 outbreak response in subnational areas in which there was co-circulation (or a high risk of co-circulation) of cVDPV2 with cVDPV1, cVDPV3 or WPV1 instead of dual mOPV2 and bOPV campaigns (35). As a result, there is still a need for all current formulations of OPV.

Live vaccines prepared from Sabin poliovirus strains of types 1, 2 and 3 were introduced for large-scale immunization in 1959. In 1972, Sabin proposed that WHO should become the custodian of his poliovirus seed strains. The Director-General of WHO agreed to assume responsibility for ensuring the proper use of the strains, and established the Consultative Group on Poliomyelitis Vaccines to advise WHO on all matters pertaining to their use. Detailed information on the work of the Consultative Group and on the preparation of the seed stocks made by Behringwerke has been published (36). NRAs should decide on the use of virus strains and on the detailed procedures applicable to the preparation of virus seed lots for the production of OPV in their own countries.

---

10 https://polioeradication.org/
The Sabin Original (SO) poliovirus seeds (26) were sent on to Merck which generated seeds designated as Sabin Original Merck (SOM). Aliquots of SOM were supplied to a number of other manufacturers to enable them to develop their own seeds. Some seed lots were contaminated with SV40 which had been present in the primary monkey kidney cells that were the preferred cell culture system at that time for virus propagation. OPV manufacturers used various strategies to reduce the contamination, including passage in the presence of specific antibody, treatment with toluidine blue and thermal inactivation of SV40 in the presence of 1M MgCl₂ that stabilizes poliovirus. In 1974 Behringwerke AG of Marburg/Lahn, Germany generously agreed to produce SO+1 seeds for WHO free of charge. The Behringwerke type 1 and type 2 seeds have been widely used from the 1970s up to the present time. In the 1950s, it had been established that, particularly for the type 3 strain, an increase in passage number correlated with increased reactivity in the MNVT. This finding led to the establishment of rigorous limits on the passage level used for vaccine production for all types.

In order to develop a more stable type 3 strain, a new seed was prepared by Pfizer from a single plaque after transfecting susceptible cells with viral RNA extracted from poliovirus at the SO+2 level. This also reduced any residual risk of SV40 contamination. One plaque (designated 457-III) was identified with particularly favourable properties (25). Theoretically, vaccine derived from this stock was at passage SO+7. However, the purpose of tracking the passage history of seed viruses is to reduce the accumulation of mutations that occur during their serial propagation. Since plaque purification represents the cloning of a single infectious particle, it eliminates the heterogeneity of the viral population and the passage level is effectively reset to zero. Thus, the cloned stock 457-III was renamed RNA-plaque-purified Sabin Original (RSO). Two additional passages were used to prepare virus master seeds (RSO+1) and working virus seeds (RSO+2), with vaccines produced from this virus at RSO+3 level. Retrospectively, the consensus sequence of RSO has been shown to be the same as the consensus sequence of SO (37) but it is more homogeneous and contains lower quantities of viruses with sequence polymorphisms. Consensus sequences of all three Sabin strains are available in GenBank under accession numbers AY184219, AY184220 and AY184221.

The RSO seed was not used for the production of type 3 vaccine until the 1980s when it became clear that the virus stocks passaged from the SOM and other SO+1 seeds were inadequate. Since then, it has been widely used by European and American manufacturers as it is of lower virulence in laboratory tests than the SO+1 type 3 seed. The RSO seeds were bought from Pfizer by Sanofi Pasteur (formerly Institut Mérieux, Pasteur Mérieux Connaught and subsequently Aventis Pasteur) which then donated them to WHO.
The virus seeds available from WHO (“WHO master seeds”) are therefore types 1 and 2 at SO+1 level produced by Behringwerke from SO seeds and the type 3 RSO “Pfizer” seed donated by Sanofi Pasteur. The seeds are kept at the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom, and the U.S. Food and Drug Administration Center for Biologics Evaluation and Research (CBER) in the United States, and include a proportion of the stocks of the SO+1 seeds formerly held at Istituto Superiore di Sanità in Italy which kindly transferred them (25, 36). These virus seed stocks are available to vaccine manufacturers upon request to WHO.

In addition to the RSO type 3 seed, a number of manufacturers in China, Japan and the Russian Federation have used their own purified seed stocks of Sabin 3 strain that were derived by a combination of passage and plaque purification (cloning). Sequencing of these seed viruses demonstrated that, while they contained low quantities of neurovirulent mutants, there were differences at other genomic sites between these strains and the consensus sequence of SO virus in the form of single nucleotide polymorphisms (SNPs) (36). However, there are no reports of any differences in clinical safety or immunogenicity between OPV produced from Pfizer stocks and from the alternative seeds of Sabin 3 virus. An overview of virus seeds used in OPV production is given below in Appendix 1.

The MNVT described in the 1989 WHO Requirements (5) has been used as a quality control test and is based on the level and distribution of virus-specific lesions within the central nervous system produced by vaccine virus upon intraspinal inoculation into the anterior horns of rhesus or cynomolgus monkeys compared against an appropriate reference preparation (38). Because nonhuman primates are used, efforts to complement and eventually replace the test are of considerable importance. WHO has encouraged and supported research on various aspects of poliovirus biology, including the development of alternative animal models, as part of the WHO initiative to promote the development of new norms and standards for vaccines. Two groups of scientists have developed transgenic (TgPVR) mice by introducing the human gene encoding the cellular receptor for poliovirus into the mouse genome (39, 40). This receptor, known as CD155, renders TgPVR mice susceptible to poliovirus infection, with clinical signs of flaccid paralysis along with histological lesions in the central nervous system similar to those observed in monkeys.

In 1992, WHO initiated a project to evaluate the suitability of transgenic mice for neurovirulence testing of OPV with the aim of replacing such testing in monkeys. The advantages of neurovirulence testing in transgenic mice include:

- a reduction in the number of primates used in the quality control of OPV;
- the use of animals of highly defined genetic and microbiological quality standards;
- a reduction in the hazards to laboratory personnel associated with handling primates; and
- a reduction in the time and cost of quality control tests for OPV.

Studies were carried out initially on type 3 mOPV using the TgPVR21 mouse line generously provided free of charge for the study by the Central Institute for Experimental Animals in Japan. Researchers at CBER developed an intraspinal inoculation method suitable for testing vaccine lots. The method was then evaluated in an international collaborative study (41) and the results assessed by WHO during a series of meetings held between 1995 and 1999. As a result of these studies, the revised WHO Recommendations for the production and control of poliomyelitis vaccine (oral) (9) introduced the murine model as an alternative to the MNVT for type 3 poliovirus. Further studies subsequently demonstrated that this test was also suitable as an alternative to the MNVT for poliovirus types 1 and 2 (12). In all cases, laboratories must comply with specifications for the containment of transgenic animals (42).

The molecular mechanisms and genetic determinants of attenuation and reversion to virulence of all three types of Sabin polioviruses used for the manufacture of OPV have been the subject of several studies. As discussed above in the context of nOPV, evidence strongly suggests that mutations in domain V of the internal ribosome entry site in the 5’ UTR of the poliovirus genome are critical determinants of attenuation and reversion (43). To quantify reversion at the molecular level, the MAPREC assay was developed by researchers at CBER (44). Studies showed that all batches of type 3 OPV contained measurable amounts of revertants, with C instead of U at nucleotide 472. Batches that failed the MNVT contained significantly higher quantities of 472-C than batches that passed the test. The CBER MAPREC studies identified 100% of vaccine lots that failed the MNVT (45).

In 1991, WHO initiated a series of international collaborative studies to evaluate the MAPREC assay for use with all three types of polioviruses and to validate appropriate international reference materials. Study results were assessed by WHO at two meetings held in 1995 and 1997 and it was concluded that the MAPREC assay was a sensitive, robust and standardized molecular biological assay suitable for use by manufacturers and NRAs for monitoring the consistency of OPV3 production. As a result, the subsequently revised WHO Recommendations for the production and control of poliomyelitis vaccine (oral) (9) introduced the MAPREC assay as the in vitro test of preference for OPV3 in place of the rct40 test. In addition, international reference materials for the MAPREC assay were established for all three serotypes. For type 3, the WHO international standard defines the threshold of 472-C content above which vaccine lots will have a high probability of failing the MNVT. Reference materials
Annex 2

for type 1 and type 2 are used to provide a measure of production consistency, but do not define the pass/fail threshold because the amount of domain V mutants that would cause the vaccine preparations to fail the MNVT is much higher than the amount found in production lots.

High-throughput sequencing (HTS), also known as deep sequencing or next generation sequencing, is a powerful technique with potentially numerous applications in the regulation of biological products. Classical (Sanger) sequencing determines the consensus or average sequence of a population of nucleic acid molecules, whereas HTS determines the sequence of individual molecules in a population. HTS generates multiple reads of each base position and produces large amounts of sequence data very rapidly. Although the technology is still evolving rapidly, determining the sequence of complete viral genomes is relatively straightforward, and usually involves amplifying sequences by polymerase chain reaction (PCR) using primers which may be either specific for a given sequence or random to pick up any nucleic acid sequence present. HTS could therefore be used in principle to detect adventitious agents whose presence was not even suspected. As HTS determines the sequence of individual molecules, it will also detect minority populations and polymorphisms so that revertants can be accurately quantitated. HTS therefore has applications in the quality control of live vaccines and could reduce the need for in vivo testing by demonstrating consistency of production on a previously impossible scale.

The bioinformatic analysis required for HTS is significant and the validation of the method for a specific purpose remains a major issue. However, it would be possible to determine if the frequency of a particular mutation – that is, a single nucleotide polymorphism (SNP) – varied between production runs. It remains to be determined to what extent this occurs and what limits could be allowed for the runs to be acceptable. In the context of OPV, HTS could be a replacement for MAPREC when used to monitor the frequency of one or two particular mutations, and studies are underway to validate this application. Early evidence indicates that HTS can be used to accurately measure the 472-C content of type 3 OPV lots and could provide an alternative to the MAPREC assay (46, 47). Whole genome HTS has the potential to become a unique tool for determining product consistency and has already been extensively applied during nOPV development, where it is a potentially more sensitive procedure for monitoring product consistency than animal neurovirulence testing.

Further developmental work needs to be completed before HTS can be introduced for general regulatory purposes. At its meeting in 2019, the WHO Expert Committee on Biological Standardization recommended that a study be performed to explore the utility of HTS technology for the quality control of OPV made from Sabin strains. Study results indicated that HTS could accurately quantify 472-C mutants in monovalent bulks of OPV3 and in the final
product (48). A second phase of the same study showed that HTS could also accurately quantify mutations of 480-A/525-C and 481-G for OPV1 and OPV2, respectively (49). The results generated by HTS and MAPREC methods were very well correlated (48–50) indicating that HTS could in principle be used as an alternative to MAPREC, providing an appropriate test format and analytical processes for establishing assay validity and pass/fail criteria were agreed with the NRA.

HTS makes it possible to conduct whole-genome sequencing on a routine basis. The degree of sequence heterogeneity expressed in terms of the number of SNPs at nucleotide positions in the genome not necessarily linked to any tangible biological properties provides a unique molecular “fingerprint” for a particular virus preparation. HTS is thus ideally suited to generating quantitative whole-genome SNP profiles of individual vaccine lots that can be used to identify types of polio seed virus and monitor consistency of manufacture. After appropriate validation and the establishment of manufacturing consistency, quantitative whole-genome SNP profiles of OPV lots could be used for routine lot release instead of the MNVT or TgmNVT. In all cases, appropriate acceptance criteria would need to be approved by the NRA.

The manufacturer of the final lot must be responsible for ensuring conformity with all recommendations applicable to the final vaccine (see sections A.5–A.11 below) even where manufacturing involves only the filling of final containers with vaccine obtained in bulk form from another manufacturing establishment. The manufacturer of the final lot must also be responsible for any production and control tests performed by an external contract laboratory, if applicable, with the approval of the NRA.

OPV has been in worldwide use since the 1960s and experience has shown that human diploid cells, primary monkey kidney cells and continuous cell lines derived from them (Vero cells) can be used to produce safe and effective vaccines.

In 1986, a WHO study group (7) concluded that the risks posed by residual cellular DNA (rcDNA) in vaccines produced in continuous cell lines should be considered to be negligible for preparations given orally. This conclusion was based on the finding that polyoma virus DNA was not infectious when administered orally (51). For such products, the principal requirement is the elimination of potentially contaminating viruses. Additional data on the uptake of DNA via the oral route have been published (52). These studies demonstrated that the efficiency of uptake of DNA introduced orally was significantly lower than that of DNA introduced intramuscularly. Nevertheless, the specifics of the manufacturing process and the formulation of a given product should be considered by NRAs (23) and, where possible, data should be accumulated on the levels of rcDNA in OPV produced in Vero cells.
International reference materials

A number of WHO international reference materials are available to help ensure that the manufacture and quality control testing of OPVs meet appropriate regulatory requirements.

WHO international standards for the potency testing of tOPV have been available since 1995. More recent WHO international standards have also been established for bOPV, mOPV1, mOPV2 and mOPV3, with compositions and potencies similar to the vaccines needed for the final phase of the GPEI. Additionally, low-titre monovalent type 1, 2 and 3 poliovirus WHO reference reagents are available for use by reference laboratories to measure the sensitivity of cell cultures to poliovirus infection. A WHO international standard for anti-poliovirus types 1, 2 and 3 antibodies (human) is also available for the standardization of neutralizing antibody tests for poliovirus.

In addition, WHO international standards for MAPREC analysis of poliovirus types 1, 2 and 3 (Sabin) and WHO international reference reagents for the control of MAPREC assays of poliovirus type 1, 2 and 3 (Sabin) are available. Some of these reference materials might be appropriate for use in HTS assays for Sabin OPV upon suitable validation. Alternatively, new reference materials may be needed for this purpose.

Reference preparations at the SO+2 passage level – designated WHO/I for type 1 virus, WHO/II for type 2 virus and WHO/III for type 3 virus – are available upon request through WHO. These reference preparations are intended for use during in vivo neurovirulence testing of OPV, both in monkeys and transgenic mice. The relevant reference preparation should be included in each vaccine test (see section A.4.4.7.2 below). Virus panels for the validation and implementation of transgenic mouse neurovirulence testing, as specified in the relevant WHO SOP, are also available.

New non-pathogenic, hyper-attenuated S19 strains of all three serotypes of poliovirus are available for conducting neutralization assays. S19 strains are polioviruses that replicate in tissue culture but are unlikely to replicate in humans, even in those exposed to large amounts, and for this reason can be used outside GAPIV containment requirements.

Some of the reference preparations developed for Sabin OPV might also be suitable for nOPV assays following suitable validation but the establishment of nOPV-specific reference preparations may be required.

The above reference materials are available from MHRA. Full details of these materials, including literature references, are provided in Appendix 8.

11 Available at: https://www.who.int/publications/m/item/neurovirulence-test-sop-of-types-1-2-or-3-opv-in-transgenic-mice-susceptible-to-poliovirus-v8.
Part A. Manufacturing recommendations

A.1 Definitions

A.1.1 International name and proper name

The international name should be “poliomyelitis vaccine (oral, live, attenuated)” with additions to indicate the virus serotype or serotypes of the vaccine and whether the vaccine is a novel or Sabin OPV. The proper name should be the equivalent of the international name in the language of the country in which the vaccine is licensed.

The use of the international name should be limited to vaccines that satisfy all of the recommendations formulated below.

A.1.2 Descriptive definition

Poliomyelitis vaccine (oral, live, attenuated) is a preparation of live attenuated poliovirus types 1, 2 or 3 grown in in vitro cultures of suitable cells containing any one type or any combination of the three types of the Sabin strains or novel genetically stabilized attenuated strains, presented in a form suitable for oral administration, and satisfying all of the recommendations set out below, as applicable.

A.2 General manufacturing recommendations

The general guidance provided in WHO good manufacturing practices for pharmaceutical products: main principles (53) and WHO good manufacturing practices for biological products (22) should apply in establishments where OPV is manufactured, with the addition of the following recommendations:

- The production of OPV should be conducted by staff who are healthy and who are examined medically at regular intervals. Steps should be taken to ensure that all individuals in the production areas are immune to poliomyelitis. Personnel working in monkey quarters should also be examined for tuberculosis as outlined in Part A, section 2 of the WHO Recommendations to assure the quality, safety, and efficacy of BCG vaccines (54).
- The establishment should be in compliance with the current global recommendations for poliovirus containment (16–18, 55).

A.3 Control of source materials

General production precautions, as described in WHO good manufacturing practices for biological products (22) should apply to the manufacture of OPV, with the additional recommendation that during production only one type of cell should be introduced or handled in the production area at any given time.
A.3.1 **Cell lines**

Some licensed OPV products are produced in primary monkey kidney cells (see Part E below). However, new OPV manufacturers are encouraged to use cell lines such as MRC-5 and Vero cells for vaccine production (23).

A.3.1.1 **Master cell bank (MCB) and working cell bank (WCB)**

The use of a cell line for OPV manufacture should be based on the cell bank system. The cell seed and cell banks used should comply with the WHO Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks (23). The cell bank should be approved by the NRA. The maximum number of passages (or population doublings) allowed between the cell seed, the MCB, the WCB and the production passage level should be established by the manufacturer and approved by the NRA. Additional tests may include, but are not limited to, propagation of the MCB or WCB cells to or beyond the maximum in vitro age for production, and examination for the presence of retrovirus and tumorigenicity in an animal test system (23).

It is important to show that the cell banks (cell seed, MCB and WCB) are free from adventitious agents relevant to the species used in their derivation. Cell banks should be assessed to confirm the absence of adventitious agents that can be inadvertently introduced during their production.

The WHO Vero reference cell bank 10-87 is considered suitable for use as a cell seed for generating an MCB (23) and is available to manufacturers on application to the Group Lead, Norms and Standards for Biologicals, Technical Specifications and Standards, Department of Health Product Policy and Standards, Access to Medicines and Health Products Division, World Health Organization, Geneva, Switzerland.

A.3.1.2 **Identity test**

Identity tests on the MCB and WCBs should be performed in accordance with the WHO Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks (23).

The cell banks should be identified using tests such as biochemical tests, immunological tests, cytogenetic marker tests and DNA fingerprinting or sequencing (23). The tests used should be approved by the NRA.

A.3.1.3 **Cell culture medium**

Serum used for the propagation of cells should be tested to demonstrate freedom from bacterial, fungal and mycoplasmal contamination using appropriate tests.
– as specified in Part A, sections 5.2 (56) and 5.3 (57) of the WHO General requirements for the sterility of biological substances – as well as freedom from infectious viruses. Suitable tests for detecting viruses in bovine serum are given in Appendix 1 of the WHO Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks (23).

Validated molecular tests for bovine viruses may replace the cell culture tests of bovine sera if approved by the NRA. As an additional monitor of quality, sera may be examined for freedom from bacteriophages and endotoxin. Gamma irradiation may be used to inactivate potential contaminant viruses, while recognizing that some viruses are relatively resistant to gamma irradiation.

The source(s) of animal components used in the culture medium should be approved by the NRA. These components should comply with the current WHO guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products (58).

Human serum should not be used. If human serum albumin derived from human plasma is used at any stage of product manufacture, the NRA should be consulted regarding the relevant requirements, as these may differ from country to country. At a minimum, it should meet the WHO Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (59). In addition, human albumin should also comply with the current WHO guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products (58).

Penicillin and other beta-lactams should not be used at any stage of manufacture, as they are highly sensitizing substances. If well justified, other antibiotics may be used during early stages of production, and should be cleared during the downstream manufacturing process. Clearance should be demonstrated through a residual removal study (or studies) and acceptable residual levels should be approved by the NRA (22).

Nontoxic pH indicators may be added – for example, phenol red at a concentration of 0.002%.

Only substances that have been approved by the NRA may be added.

Bovine or porcine trypsin used for preparing cell cultures should be tested and found to be free of cultivable bacteria, fungi, mycoplasmas and infectious viruses, as appropriate (23). The methods used to ensure this should be approved by the NRA.

In some countries, irradiation is used to inactivate potential contaminant viruses in trypsin. If irradiation is used, it is important to ensure that a reproducible dose is delivered to all batches and to the component units of each batch. The irradiation dose must be low enough so that the biological properties of the reagents are retained while being high
enough to reduce viral contamination. Therefore, irradiation cannot be considered a sterilizing process (23). The irradiation method should be validated by the manufacturer and approved by the NRA.

Recombinant trypsin is available and OPV manufacturers are encouraged to use it due to the reduced risk of contamination compared to animal-sourced trypsin – however, it should not be assumed to be free of the risk of contamination and should be subject to the usual considerations for any reagent of biological origin (23).

The source(s) of trypsin of bovine origin, if used, should be approved by the NRA and should comply with the current WHO guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products (58).

A.3.2 Virus seeds

A.3.2.1 Virus strains

Strains of poliovirus used in the production of OPV should be identified by historical records. These should include information on strain origin and subsequent manipulation or passage, including any recombinant DNA technology steps used to modify the viral genome, when applicable.

In addition, it is recommended that the presence of sequence heterogeneities across the entire genome of an OPV virus strain is determined by HTS and documented as a reference for future characterization of the virus seed lots.

Producers of Sabin OPV can obtain virus master seeds from WHO. Manufacturers receiving this virus master seed may prepare a sub-master seed by a single passage and then prepare their working seed from the characterized sub-master seed. Currently, nOPV strains are only available from the respective developers.

Only virus strains approved by the NRA should be used (see General considerations above).

A.3.2.2 Virus seed lot system

Vaccine production should be based on the seed lot system. Virus seed lots should not be purified. The virus working seed lot used for the production of vaccine batches should be prepared by a single passage from the virus master seed lot or the virus sub-master seed lot (if used) using a method, and at a passage level from the original seed virus, approved by the NRA.

Virus master, sub-master and working seed lots should be stored as recommended in WHO good manufacturing practices for biological products (22) – for example, in temperature-monitored freezers at −60 °C or below to
ensure stability on storage. Guidance on the additional characterization of master and sub-master seeds is provided below in Part B.

A.3.2.3 Tests on virus master, sub-master and working seed lots

The Sabin virus master seeds provided by WHO are well characterized and can be used to prepare sub-master seeds using the approved process. All other virus seed lots used for the production of OPV batches (including any sub-master seed derived from the WHO master seed) should be subjected to the tests listed in this section and should conform to the recommendations set out below in sections A.4.3 (single harvests) and A.4.4.1–A.4.4.4 (monovalent bulks). The control cell cultures for virus seed production should conform to section A.4.1 below (control of cell cultures).

A.3.2.3.1 Tests for adventitious viruses and freedom from detectable SV40 sequences

The virus seed lots should be shown to be free from detectable adventitious viruses and from detectable SV40 DNA when applicable as determined by a validated nucleic acid amplification technique (NAT)-based assay. The need to test for SV40 DNA, and other human, simian, bovine or porcine adventitious agents, should be based on risk assessment of potential contamination of the cell substrates used to propagate the virus, as well as the risk of adventitious agents being inadvertently introduced through the use of raw materials – for example, animal-derived culture medium components. If necessary, viruses such as bovine polyomavirus, porcine parvovirus and porcine circovirus should be screened for using specific assays, such as molecular NAT-based assays (23).

SV40 DNA is widely used as a molecular biological reagent and the contamination of PCR assays is potentially a major problem. One approach is to identify separate genomic regions of SV40 for amplification and to use one region for screening purposes and the other for the confirmation of repeatedly positive samples. It is useful if the second genomic region used for confirmation varies between isolates from different sources, as it is then possible to show that it has a unique sequence and that positive results are not due to contamination with laboratory strains of SV40. The sensitivity of the PCR assays for the genomic regions used should be established.

New molecular methods with broad detection capabilities are being developed for the detection of adventitious agents. These methods include: (a) degenerate NAT for whole virus families, with analysis of the amplicons by hybridization, sequencing or mass spectrometry; (b) NAT with random primers followed by analysis of the amplicons on large oligonucleotide microarrays of conserved viral sequencing, or digital subtraction of expressed sequences; and (c) HTS. These methods might
be used in the future to supplement existing methods or as alternative methods to both in vivo and in vitro tests after appropriate validation and with the approval of the NRA (23).

The testing strategy for adventitious virus(es) in seed lots should be based on risk assessment. However, sterility testing for bacteria, fungi and mycoplasmas should always be conducted.

A.3.2.3.2 In vitro tests to monitor virus molecular consistency

New virus seed lots used for OPV production should be evaluated for molecular consistency using a suitable test (such as an HTS assay) and should meet the acceptance criteria approved by the NRA. Virus seeds prepared from Sabin strains may be evaluated using the MAPREC assay and should meet the acceptance criteria described below in section A.4.4.7.1. In addition, at least three consecutive monovalent bulks prepared from the new seed virus should meet the acceptance criteria of the applicable in vitro test described in section A.4.4.7.1. Where an HTS assay is used it should be validated using appropriate standards and materials, and acceptance criteria approved by the NRA. At this point, the use of HTS remains developmental and is the subject of international collaborative evaluation that may result in the establishment and availability of appropriate reference materials with defined acceptance criteria.

The acceptance criteria for percentage of mutations at positions that are not examined by MAPREC but found to be variable under the conditions used by the manufacturer should be based on the molecular characteristics of vaccine batches shown to be safe and immunogenic in clinical studies. The acceptance criteria of an HTS assay should be updated periodically based on manufacturing experience. Acceptance criteria should be approved by the NRA.

nOPV seeds and at least three consecutive monovalent bulks prepared from each new working seed should be characterized using an HTS assay, with particular attention given to the regions of the genome that are modified in the parental nOPV strain compared to the Sabin OPV strain. The genetic modifications introduced in domain V of the 5’ UTR of nOPV include changes in specific base pairs of the hairpin structure where GC and GU pairs are replaced by AU base pairs. Strengthening of the hairpin structure leading to neuroviral reversion would require two simultaneous mutations, and the frequency of such double reversions should be minimal. HTS analysis should therefore be conducted to ensure the absence of undesirable modifications in the 5’ UTR, with particular attention given to changes in base pairing in domain V.
A.3.2.3.3  Neurovirulence tests for virus seeds prepared from Sabin strain

New virus seeds prepared from Sabin strains (with the exception of the well-characterized WHO master seed) should be evaluated for neurovirulence using the MNVT or TgmNVT. Summaries of the MNVT and TgmNVT, including pass/fail criteria, are given below in Appendix 2 along with considerations in the choice of assay. The test used should be approved by the NRA for the specific product.

The test for neurovirulence in nonhuman primates should be carried out as summarized in Appendix 2 and following the WHO SOP for the neurovirulence test of types 1, 2 or 3 live attenuated poliomyelitis vaccines (oral) in monkeys, available from WHO.\(^{13}\)

Under normal circumstances, a new virus working seed will be prepared using the same production protocol and from the same virus master seed or sub-master seed as the currently approved virus working seed. If the TgmNVT has been approved by the NRA for the release of vaccine batches, and if the virus working seed is generated by the same production process, the new seed can be qualified by use of the transgenic mouse test and supporting in vitro data alone. The TgmNVT should be carried out as summarized in Appendix 2 and following the WHO SOP for the neurovirulence test of types 1, 2 or 3 live attenuated poliomyelitis vaccines (oral) in transgenic mice susceptible to poliovirus.\(^{14}\)

Where there are any major changes in the production process for a new virus working seed or virus sub-master seed, full characterization using an in vivo neurovirulence test and HTS assay will be required (see Part B below).

The neurovirulence of the virus working seed, and of at least three consecutive monovalent bulks prepared from it, should meet the criteria for acceptability given in section A.4.4.7.2 below and in the appropriate SOP before the virus working seed can be considered suitable for use in the production of OPV with the agreement of the NRA.

A.3.2.3.4  Neurovirulence tests for nOPV virus seeds

The virus seed lot used for nOPV production should be evaluated for neurovirulence. The testing strategy (for example, testing of master virus seed and/or working virus seed) and the method selected (MNVT and/or TgmNVT) should be approved by the NRA. The in vivo neurovirulence test should be carried out as summarized in Appendix 2 below and in the applicable SOP

\(^{13}\) Available at: https://www.who.int/publications/m/item/neurovirulence-test-of-types-1-2-or-3-opv-in-monkeys.

\(^{14}\) Available at: https://www.who.int/publications/m/item/neurovirulence-test-sop-of-types-1-2-or-3-opv-in-transgenic-mice-susceptible-to-poliovirus-v8.
Annex 2

available from WHO.15 The current WHO reference preparation for the MNVT derived from Sabin strain (see Appendix 8 below) is suitable for evaluating the neurovirulence of nOPV virus seeds and vaccine batches.

It is likely that molecular assays will be more sensitive than the animal tests used to justify the limits chosen. All nOPV producers should generate data to support the replacement of in vivo neurovirulence tests with HTS for evaluating neurovirulence in nOPV seeds and vaccine batches by examining the entire genome. The acceptance criteria for percentage of mutations should in the first instance be based on the molecular characteristics of vaccine batches shown to be safe in clinical studies and that have met the in vivo neurovirulence test acceptance criteria. Specifications are likely to change with experience. The data generated will be used to demonstrate consistency and in the longer term the acceptable limits should be set on this basis.

A.4  Control of vaccine production

For OPV prepared in cultures of primary monkey kidney cells, Part E below provides additional or alternative recommendations regarding the testing of the cell substrate used for vaccine production. The guidance provided in Part E should therefore be added to – or used as an alternative to – the relevant guidance provided in this section.

A.4.1  Control cell cultures

When human diploid or continuous cell lines are used to prepare cultures for the production of vaccine, a fraction equivalent to at least 5% of the total or 500 mL of cell suspension or 100 million cells – at the concentration and cell passage level employed for seeding vaccine production cultures – should be used to prepare control cultures. An example flowsheet of the cell culture tests performed during OPV production using cell banks is provided below in Appendix 3.

If bioreactor technology is used, the NRA should determine the size and treatment of the cell sample to be examined.

A.4.1.1  Tests of control cell cultures

The treatment of the cells set aside as the control material should be similar to that of the production cell cultures, but they should remain uninoculated for use as control cultures for the detection of adventitious agents.

The control cell cultures should be incubated under conditions as similar as possible to the inoculated cultures for at least 2 weeks and should be tested for

---

the presence of adventitious agents as described below. For the test to be valid, not more than 20% of the control cell cultures should have been discarded for any reason by the end of test period.

At the end of the observation period, the control cell cultures should be examined for evidence of degeneration caused by an adventitious agent. If this examination, or any of the tests specified in this section, shows evidence of the presence of any adventitious agent in the control culture, the poliovirus grown in the corresponding inoculated cultures should not be used for vaccine production.

If not tested immediately, samples should be stored at −60 °C or below.

A.4.1.2 Tests for haemadsorbing viruses

At the end of the observation period, at least 25% of the control cells should be tested for the presence of haemadsorbing viruses using guinea-pig red blood cells. If the latter cells have been stored, the duration of storage should not have exceeded 7 days and the storage temperature should have been in the range 2–8 °C. In tests for haemadsorbing viruses, calcium and magnesium ions should be absent from the medium.

Some NRAs require that, as an additional test for haemadsorbing viruses, other types of red blood cells, including cells from humans, monkeys and chickens (or other avian species), should be used in addition to guinea-pig cells.

A reading should be taken after incubation at 2–8 °C for 30 minutes, and again after further incubation for 30 minutes at 20–25 °C.

If a test with monkey red blood cells is performed, readings should also be taken after a final incubation for 30 minutes at 34–37 °C.

In some countries the sensitivity of each new lot of red blood cells is demonstrated by titration against a haemagglutinin antigen before use in the test for haemadsorbing viruses.

A.4.1.3 Tests for other adventitious agents in cell supernatant fluids

At the end of the observation period, a sample of the pooled supernatant fluid from each group of control cultures should be tested for adventitious agents. For this purpose, 10 mL of each pool should be tested in the same cells, but not the same batch of cells, as those used for the production of vaccine.

A second indicator cell line should be used to test an additional 10 mL sample of each pool. When a human diploid cell line is used for production, a simian kidney cell line should be used as the second indicator cell line. When a simian kidney cell line is used for production, a human diploid cell line should be used as the second indicator cell line (23).
The pooled fluid should be inoculated into culture vessels of these cell cultures in such a way that the dilution of the pooled fluid in the nutrient medium does not exceed 1 part in 4. The area of the cell monolayer should be at least 3 cm² per mL of pooled fluid. At least one culture vessel of each kind of cell culture should remain uninoculated and should serve as a control.

The inoculated cultures should be incubated at a temperature of 35–37 °C and should be observed for at least 14 days.

Some NRAs require that, at the end of this observation period, a subculture is made in the same culture system and observed for at least an additional 14 days. Furthermore, some NRAs require that these cells should be tested for the presence of haemadsorbing viruses.

For the tests to be valid, not more than 20% of the culture vessels should have been discarded for any reason by the end of the test period.

If any cytopathic changes due to adventitious agents occur in any of the cultures, the virus harvests produced from the batch of cells from which the control cells were taken should be discarded.

Some selected viruses may be screened for using specific validated assays approved by the NRA – such as assays based on molecular techniques (for example, NAT or HTS) (23).

If these tests are not performed immediately, the samples should be kept at a temperature of −60 °C or below.

A.4.1.4 **Identity test**

At the production level, the cells should be identified by means of tests approved by the NRA. Suitable methods include, but are not limited to, biochemical tests (for example, isoenzyme analyses), immunological tests, cytogenetic tests (for example, for chromosomal markers) and tests for genetic markers (for example, DNA fingerprinting or sequencing).

A.4.2 **Cell cultures for vaccine production**

A.4.2.1 **Observation of cultures for adventitious agents**

On the day of inoculation with the virus working seed lot, each cell culture or a sample from each culture vessel should be examined visually for degeneration caused by infective agents. If such examination shows evidence of the presence of any adventitious agent, the culture should not be used for vaccine production.

If animal serum is used for cell cultures before the inoculation of virus, the medium should be removed and replaced with serum-free maintenance medium after the cells have been washed with serum-free medium.
A.4.3 Control of single harvests

A.4.3.1 Single harvest

After inoculation of the production cells with the virus working seed lot, inoculated and control cell cultures should be held at a fixed temperature that has been shown to be suitable – for example, within the range 33–35 °C for Sabin strains. The temperature range required to produce a consistent satisfactory product for nOPV manufacture may be different and should be validated.

The temperature should be controlled within a narrow range (for example, ± 0.5 °C from the set temperature). The optimal range for pH, multiplicity of infection, cell density, duration of incubation, and time of virus recovery should be established by each manufacturer and should be approved by the NRA.

The incubation time of the viral culture should be established and validated for each OPV during product development. The virus suspension of Sabin strain should be harvested not later than 96 hours after virus inoculation to limit the number of replication cycles.

Similar appropriate limits should be investigated and set for nOPV harvests.

The inoculated cell cultures should be processed in such a way that each virus suspension harvested remains identifiable as a single harvest and is kept separate from other harvests until the results of all the tests described in sections A.4.1.2–A.4.1.4 and sections A.4.3.3.1–A.4.3.3.5 have been obtained. If pooling of single harvests takes place before all the testing results become available, the practice should be justified and a procedure should be put in place to ensure that a monovalent bulk is discarded if any one of the pooled single harvests does not meet all the approved specifications.

A.4.3.2 Sampling

The samples required for the testing of single harvests should be taken immediately upon harvesting. If the tests for adventitious agents as described below in section A.4.3.3.3 are not performed immediately, the samples taken for these tests should be kept at a temperature of −60 °C or lower and subjected to no more than one freeze–thaw cycle.

A.4.3.3 Tests on single harvest

A.4.3.3.1 Identity

Each single harvest should be identified using a suitable method, such as an immunological assay on cell culture using specific antibodies or a molecular method that has been validated and approved by the NRA. If the virus seeds used for production and other poliovirus strains are manipulated or stored at the same production facilities, the identity test should be able to distinguish between these strains as well as distinguish between different poliovirus serotypes.
Neutralization tests can distinguish the serotypes of poliovirus. Molecular methods such as sequencing, HTS or qPCR can distinguish different strains and serotypes of poliovirus.

Care should be taken to ensure that the sera used are monospecific by titrating them against homotypic and heterotypic viruses of known virus titre. Monoclonal antibodies may be useful in this test.

A.4.3.3.2 Titration for virus content

The virus titre per mL of single harvest should be determined in cell cultures in comparison with an existing reference preparation (see Appendix 4), and the result should meet the specification approved by the NRA.

A.4.3.3.3 Tests of neutralized single harvests for adventitious agents

For the purposes of the recommendations set out in this section, the volume of each single harvest sample taken for neutralization and testing should be at least 10 mL and should be such that a total of at least 50 mL or the equivalent of 500 doses of final vaccine, whichever is the greater, has been withheld from the corresponding single harvest.

The antisera used for neutralization should be of nonhuman origin and should have been prepared in animals other than monkeys using virus cultured in cells from a different species to that used in the production of the vaccine. Samples of each virus harvest should be tested in human cells and at least one other sensitive cell system.

The neutralized suspensions should be inoculated into bottles of these cell cultures in such a way that the dilution of the suspension in the nutrient medium does not exceed 1 part in 4. The area of the cell sheet should be at least 3 cm² per mL of neutralized suspension. At least one bottle of each kind of cell culture should remain uninoculated and should serve as a control – the control should be maintained using nutrient medium containing the same concentration of the specific antiserum used for neutralization.

Animal serum may be used in the propagation of the cells, but the maintenance medium used after inoculation of the test material should contain no added serum other than the poliovirus neutralizing antiserum or fetal calf serum of controlled origin.

The inoculated cultures should be incubated at a temperature of 35–37 °C and should be observed for at least 14 days.

If adequately justified and validated, lower temperatures may be used.

For the tests to be valid, not more than 20% of the culture vessels should have been discarded for any reason by the end of the test period.
If any cytopathic changes due to adventitious agents occur in any of the cultures, the virus harvest should be discarded.

New molecular methods with broad detection capabilities are being developed for the detection of adventitious agents. These methods include: (a) degenerate NAT for whole virus families with analysis of the amplicons by hybridization, sequencing or mass spectrometry; (b) NAT with random primers followed by analysis of the amplicons on large oligonucleotide microarrays of conserved viral sequencing or digital subtraction of expressed sequences; and (c) HTS. These methods might be used to supplement existing methods or as alternative methods to both in vivo and in vitro tests after appropriate validation and with the approval of the NRA (23).

A.4.3.3.4 Sterility tests for bacteria, fungi and mycoplasmas

A volume of at least 10 mL of each single harvest should be tested for bacterial, fungal and mycoplasmal contamination using appropriate tests, as specified in Part A, sections 5.2 and 5.3 of the WHO General requirements for the sterility of biological substances (56, 57), or by methods approved by the NRA.

Molecular assays (for example NAT-based assays alone or in combination with cell culture) may be used as an alternative to one or both of the compendial mycoplasma detection methods following suitable validation and with the agreement of the NRA (23).

A.4.3.3.5 Test for mycobacteria

The virus harvest should be shown to be free from mycobacteria using an appropriate method approved by the NRA.

Molecular assays (for example, NAT-based assays) may be used as an alternative to mycobacteria microbiological culture method tests for the detection of mycobacteria following suitable validation and with the agreement of the NRA (23).

Some manufacturers test for mycobacteria only at the monovalent bulk stage with the agreement of the NRA.

A.4.3.3.6 Tests for molecular consistency of production

OPV producers may monitor the molecular characteristics of single harvests or monovalent bulks using an in vitro test as described in A.3.2.3.2 above. These data may further demonstrate manufacturing consistency.
A.4.4  Control of monovalent bulk
A.4.4.1  Preparation of monovalent bulk
The monovalent bulk may be prepared by pooling a number of single harvests of the same virus serotype into a single vessel. This bulk should be filtered through a filter that is able to retain cell debris.

The NRA may require further purification of harvests derived from continuous cell lines. If the harvests are derived from human diploid or primary monkey kidney cells, further purification is not required.

A.4.4.2  Sampling
Samples of the monovalent bulk prepared as described in section A.4.4.1 above should be taken immediately and, if not tested immediately, should be kept at a temperature of −60 °C or below until the tests described in the following sections are performed.

A.4.4.3  Identity test
Each monovalent bulk should be identified using a suitable method, as described in section A.4.3.3.1 above.

A.4.4.4  Titration for virus content
The virus titre per mL of filtered monovalent bulk should be determined in cell cultures in comparison with an existing reference preparation (see Appendix 4), and the result should meet the specification approved by the NRA.

The virus titre as determined by this test should be the basis for the quantity of virus used in the neurovirulence tests in monkeys or transgenic mice (see sections A.4.4.7.2 and A.4.4.7.3 below) and for formulation of the final bulk (see section A.4.5 below).

The detailed procedures for carrying out this test and for interpreting the results should be approved by the NRA.

A.4.4.5  Sterility tests for bacteria and fungi
Each monovalent bulk should be tested for bacterial and fungal sterility as specified in Part A, section 5.2 of the WHO General requirements for the sterility of biological substances (56).

A.4.4.6  Test for mycobacteria
Each monovalent bulk should be shown to be free from mycobacteria by an appropriate method approved by the NRA.
Molecular assays (for example, NAT-based assays) may be used as an alternative to mycobacteria microbiological culture method tests for the detection of mycobacteria following suitable validation and with the agreement of the NRA (35).

A.4.4.7 Tests to monitor virus molecular characteristics (consistency)
The poliovirus in the filtered monovalent bulk, prepared as described in section A.4.4.1 above, should be tested in comparison with the seed lot or a reference virus preparation (see Appendix 8) to ensure that the vaccine virus has not undergone changes during its multiplication in the production cell culture.

A.4.4.7.1 In vitro tests to monitor virus molecular consistency
As with the virus seed lot (see section A.3.2.3.2 above), the virus in the monovalent bulk should also be tested for molecular consistency using at least one in vitro method.

A.4.4.7.1.1 MAPREC
The MAPREC assay is suitable for all three serotypes of Sabin OPV but not nOPV which should be evaluated for molecular consistency using a suitable test such as whole genome HTS. Implementation of the MAPREC assay should be fully validated by each manufacturer and performed according to the WHO SOP\textsuperscript{16} developed during WHO collaborative studies or according to a validated alternative procedure.

The MAPREC assay should be used to establish the consistency of production once the test has been validated and normal values for the standards have been established. For all Sabin OPV preparations, and depending on a laboratory’s experience with the MAPREC assay, an approach based on “warning limits” of ± 2 standard deviations and “rejection limits” of ± 3 standard deviations from the historical mean may be appropriate. Acceptance and rejection criteria should be specific to each manufacturer and each working seed and should be continually updated as each new bulk is prepared. An investigation of consistency should take place if a batch produces results that are inconsistent with previous production batches.

Results should be expressed as ratios relative to the relevant type-specific WHO international standard for MAPREC analysis of poliovirus (Sabin) (see Appendix 8). The acceptable variation in mutant content from batch to batch should be agreed with the NRA in the light of production and testing experience.

\textsuperscript{16} Available at: https://www.who.int/publications/m/item/maprec-sop-for-opv-types-1-2-or-3.
For type 3 (472-C), a batch should be rejected if the level of mutations is above 1.0% when normalized against the international standard. The limits for types 1 and 2 should be approved by the NRA.

Levels of mutations obtained by manufacturers who have implemented the test for types 1 and 2 virus have been less than 2.0% for type 1 Sabin (for the sum of both mutations 480-A and 525 C) and less than 1.5% for type 2 Sabin (481-G) (60).

If a filtered monovalent bulk fails the MAPREC assay, it cannot be used in the manufacturing of finished product, and an evaluation of the manufacturing process (including the suitability of the virus working seed) should be undertaken and discussed with the NRA. Filtered monovalent bulks that pass the MAPREC assay should be tested subsequently for in vivo neurovirulence (see section A.4.4.7.2 below).

The MAPREC assay for type 3 is highly predictive of in vivo neurovirulence in animal models. No such correlation exists for types 1 and 2 at the level of revertants present in vaccine bulks. For these types, the MAPREC assay results provide a measure of consistency (60).

Non-radioactive MAPREC methods are available and may be introduced after validation and with the approval of the NRA.

A.4.4.7.1.2 HTS

The MAPREC assay may be replaced by alternative molecular biology methods (such as HTS) that demonstrate an equivalent or better level of sensitivity following validation, and with the approval of the NRA. The current MAPREC reference materials might also be useful for HTS assays for Sabin OPV upon suitable validation. Alternatively, new reference materials might be needed for this purpose.

A.4.4.7.2 Neurovirulence tests for Sabin OPV

An appropriate in vivo test should be used to evaluate virus monovalent bulks. Summaries of the MNVT and TgmNVT, including pass and fail criteria, are given in Appendix 2 along with considerations in the choice of assay.

The test should be approved by the NRA for the specific product and may use transgenic mice or nonhuman primates or both. The test for neurovirulence in nonhuman primates should be carried out as summarized below in Appendix 2 and as described in the corresponding WHO SOP.¹⁷

¹⁷ Available at: https://www.who.int/publications/m/item/neurovirulence-test-of-types-1-2-or-3-opv-in-monkeys.
Where the TgmNVT has been approved by the NRA, it should be carried out as summarized in Appendix 2 and as described in the corresponding WHO SOP.\textsuperscript{18} Its use for batch release purposes should follow the appropriate validation and implementation processes according to national and international regulations. The WHO SOP has been validated for vaccines made from Behringwerke SO-derived seeds (types 1 and 2) and RSO seeds (type 3).

To qualify as competent to perform the TgmNVT there is a requirement for laboratories to complete a standard implementation process as detailed in the relevant WHO SOP. Once qualified as competent, each laboratory should continue to monitor its performance on a routine basis.

The WHO collaborative study demonstrated that the MNVT and TgmNVT are equivalent for testing vaccines prepared from RSO seeds but that the TgmNVT may fail otherwise acceptable (by the MNVT) lots prepared from derivative strains containing additional mutations (41). Therefore, the TgmNVT can be used as a replacement for the MNVT for vaccines made from RSO Sabin 3 strain but may require further validation for other derivative strains. This may include the development of an appropriate homologous reference preparation.

It is possible that the in vivo neurovirulence test can be omitted once manufacturing consistency has been established based on the results of both in vivo and whole genome HTS. However, additional experience and data are required to establish suitable acceptance criteria for whole genome HTS performed for the control of Sabin OPV.

A.4.4.7.3 Neurovirulence tests for nOPV

Where the results of manufacturing, preclinical and clinical studies have demonstrated the genetic stability of the attenuation to the satisfaction of the NRA, the in vivo MNVT may be omitted for routine manufacturing control of nOPV with the agreement of the NRA.

Only monovalent bulks that meet the acceptance criteria using a validated HTS assay are used to formulate the final product.

The acceptance criteria for percentage of mutations at positions found to be variable under the conditions used during manufacture should be based on the molecular characteristics of vaccine batches shown to be safe and immunogenic in clinical studies, or vaccine batches that have met the acceptance criteria of an in vivo NVT. When mutations arise at additional positions, a risk assessment should be performed to assess their potential impact on neurovirulence based on current understanding of the genetic basis for attenuation (29, 61). An in vivo NVT should be performed to assess the suitability of the monovalent bulk when required by the risk assessment. The acceptance criteria of the HTS assay

\textsuperscript{18} Available at: https://www.who.int/publications/m/item/neurovirulence-test-sop-of-types-1-2-or-3-opv-in-transgenic-mice-susceptible-to-poliovirus-v8.
should be updated periodically based on manufacturing experience, and should be approved by the NRA.

A.4.5 Final bulk
Final bulk may contain one or more serotypes of poliovirus of the same type of strain (Sabin or nOPV). The operations necessary for preparing the final bulk should be conducted in such a way as to avoid contamination of the product.

The dilution and mixing procedures involved in preparing the final vaccine bulk should be approved by the NRA.

A.4.5.1 Stabilizers
Any stabilizers that might be included in the final bulk should have been shown, to the satisfaction of the NRA, to improve the stability of the vaccine in the concentrations used and not to impair the safety of the vaccine.

All the tests described in sections A.4.3.3 and A.4.4 above should be performed on samples taken before any stabilizers are added where possible.

A.4.5.2 Sterility tests for bacteria and fungi
The final vaccine bulk should be tested for bacterial and fungal sterility, as specified in Part A, section 5.2 of the WHO General requirements for the sterility of biological substances (56).

A.5 Filling and containers
The requirements concerning filling and containers given in WHO good manufacturing practices for pharmaceutical products: main principles (53) and WHO good manufacturing practices for biological products (22) should apply to OPV filled in the final form. Single- and multi-dose containers may be used.

A final filtration may be included just before the filling operations.

The conditions for storage and shipping, as well as the shelf-life, should be supported by adequate stability data and approved by the NRA.

A.6 Control tests on the final lot
Samples should be taken from each final lot for the tests described in the following sections. The tests should be performed on each final lot of vaccine (that is, in the final containers). Unless otherwise justified and authorized, the tests should be performed on labelled containers from each final lot by means of validated methods approved by the NRA. In general, the specification used for each test of OPV final lot should be supported by the quality attributes of the clinical lots shown to be safe and sufficiently immunogenic in clinical studies and should be approved by the NRA.
A.6.1  Inspection of final containers
Every container in each final lot should be inspected visually or mechanically, and those showing abnormalities should be discarded safely according to applicable regulations. Each abnormality should be recorded.

A.6.1.1  Appearance
The appearance of the vaccine should meet the specifications approved by the NRA with respect to its form and colour.

A.6.2  Extractable volume
Unless otherwise justified and authorized, the extractable volume (in mL) and the number of drops (using the approved dropper) should be determined in a minimum of five individual final containers, and should meet the specification approved by the NRA.

A.6.3  pH
The pH of the final lot should be tested and the result should be within the range shown to be adequate for preserving virus stability.

A.6.4  Identity
An identity test should be performed on at least one labelled container from each final lot using a suitable method as described in section A.4.3.3.1.

A.6.5  Bacterial and fungal sterility
Each final lot should be tested for bacterial and fungal sterility as specified in Part A, section 5.2 of the WHO General requirements for the sterility of biological substances (56), or using methods approved by the NRA.

A.6.6  Potency
At least three final containers should be selected at random from each final lot and should be individually tested in a single assay. When the vaccine contains more than one poliovirus type, each type should be titrated separately by using appropriate type-specific antiserum to neutralize each of the other types present. The amount of poliovirus of each serotype present in the vaccine, and its total poliovirus content, should be determined. The assay should include a reference material as described below in Appendix 4. The minimum virus titre per human dose should be shown to induce an adequate immune response in clinical studies, and should be approved by the NRA.
An upper limit may be established by each manufacturer to ensure lot-to-lot consistency (for example, based on mean titre $\text{CCID}_{50} + 3$ standard deviations). The upper limit should be approved by the NRA.

Based on available data, it is recommended that the estimated mean virus titres for a single human dose of tOPV prepared from Sabin strain should be not less than $10^{6.0} \text{CCID}_{50}$ for type 1, $10^{5.0} \text{CCID}_{50}$ for type 2, and $10^{5.5} \text{CCID}_{50}$ for type 3, as determined in an assay described in Appendix 4 below. The 95% confidence intervals of the assays should not differ by a factor of more than $0.3 \log_{10}$ of the estimated number of infectious units in the vaccine. Different potency limits may be acceptable if supported by clinical data.

In 1986, the WHO Region of the Americas began to use a trivalent formulation containing $10^{5.8} \text{CCID}_{50}$ of poliovirus type 3 (62) following a study in Brazil which demonstrated improved immunogenicity when the amount of type 3 virus in the trivalent vaccine was increased (63). The subsequent success in controlling poliomyelitis in the Americas using this formulation led the Global Advisory Group for the Expanded Programme on Immunization to recommend a formulation of tOPV for use worldwide with $10^{6.0}$, $10^{5.0}$ and $10^{5.8} \text{CCID}_{50}$ per dose for types 1, 2 and 3 respectively (35, 64).

The potency specifications for nOPV should be set based on the potency of vaccine lots shown to induce adequate protective immunity in clinical trials. An upper limit should also be defined based on available human safety data.

### A.6.7 Thermal stability

Thermal stability should be considered as a vaccine characteristic that provides an indicator of production consistency. The thermal stability test is not designed to provide a predictive value of real-time stability but rather to evaluate whether the product complies with a defined stability specification. Additional guidance on the evaluation of vaccine stability is provided in the WHO Guidelines on stability evaluation of vaccines (65).

Three final containers of each final lot should be incubated at 37 °C for 48 hours. The total virus content in both exposed and unexposed containers should be determined concurrently with that of a suitable validated reference preparation. The loss of potency on exposure should be within the limit approved by the NRA.

For tOPV prepared from Sabin strain, the vaccine passes the test when the loss on exposure is not greater than a factor of $0.5 \log_{10} \text{CCID}_{50}$ per human dose. Several OPV manufacturers have demonstrated that the thermal stability test specification applied to tOPV formulations (loss on exposure is not greater than a factor of $0.5 \log_{10} \text{CCID}_{50}$ per human dose)
is not applicable to some mOPVs and bOPVs. Some manufacturers have shown that mOPV formulations that failed the current tOPV specification of $0.5 \log_{10}$ have an acceptable stability profile throughout the product shelf-life. Therefore, a specification of $0.6 \log_{10}$ has been accepted by the NRAs and by the WHO Prequalification Programme in those cases.

Suitable thermal stability test for nOPV should be established and validated.

A.6.8 **Residual antibiotics (if applicable)**

If any antibiotics are added during vaccine production, the residual antibiotic content should be determined and should be within limits approved by the NRA. This test may be omitted for routine lot release once consistency of production has been established to the satisfaction of the NRA.

A.6.9 **Stabilizer (if applicable)**

If a stabilizer is added during vaccine production, the content of the stabilizer present in the vaccine should be determined and should be within limits approved by the NRA.

A.7 **Records**

The requirements given in section 17 of WHO good manufacturing practices for biological products (22) should apply.

A.8 **Retained samples**

The requirements given in section 16 of WHO good manufacturing practices for biological products (22) should apply.

A.9 **Labelling**

The requirements given in section 14 of WHO good manufacturing practices for biological products (22) should apply.

The label on the carton, the container or the leaflet accompanying each container should include the following information:

- the designation(s) of the strain(s) of poliovirus contained in the vaccine;
- the minimum amount of virus of each type contained in one recommended human dose;
- the cell substrate used for the preparation of the vaccine, and the nature and amount of any stabilizer present in the vaccine;
Annex 2

- a statement that the vaccine is not to be injected;
- the number of doses in each vial; and
- the volume of each dose.

It is desirable for the label to carry the names both of the producer and of the source of the bulk material if the producer of the final vaccine did not prepare it. The nature and amount of the antibiotics present in the vaccine, if any, may be included.

A.10 Distribution and shipping

The requirements given in WHO good manufacturing practices for biological products (22) should apply. Further guidance is provided in the WHO Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (66).

A.11 Stability testing, storage and expiry date

A.11.1 Stability testing

Adequate stability studies form an essential part of vaccine development. These studies should follow the general principles outlined in the WHO Guidelines on stability evaluation of vaccines (65) and WHO Guidelines on the stability evaluation of vaccines for use under extended controlled temperature conditions (67). The shelf-life of the final product and the hold time of each process intermediate (such as single harvests, monovalent bulk and final bulk) should be established based on the results of real-time, real-condition stability studies, and should be approved by the NRA.

The stability of the vaccine in its final container, maintained at the recommended storage temperature up to the expiry date, should be demonstrated to the satisfaction of the NRA on at least three consecutive lots of final product. Accelerated thermal stability tests may be undertaken to provide additional information on the overall characteristics of the vaccine and may also aid in assessing comparability should the manufacturer decide to change any aspect of manufacturing.

The formulation of the vaccine should be shown to minimize potency loss throughout its shelf-life. In case of potency loss (for example, when stored at 2–8 °C for 6 months), the manufacturer should implement a higher potency limit at release to ensure that all vaccine lots released will meet the minimum potency specification at the end of shelf-life as described in the WHO Guidelines on the stability evaluation of vaccines for use under extended controlled temperature conditions (67). Acceptable limits for stability should be agreed with the NRA. Following licensure, ongoing monitoring of vaccine stability is recommended to support shelf-life specifications and to refine the stability
profile (65). The ongoing stability testing programme should be approved by the NRA and should include an agreed set of stability-indicating parameters, procedures for the ongoing collection of stability data and criteria for the rejection of vaccine(s). Data should be provided to the NRA in accordance with local regulatory requirements.

Where the vaccine is to be stockpiled, manufacturers should conduct real-time stability studies on monovalent bulks at −40 °C or below, or on finished monovalent, bivalent and trivalent compositions at −20 °C.

Any extension of the shelf-life should be based on stability data and approved by the NRA.

A.11.2 Storage conditions

Before being released by the manufacturing establishment, all vaccines in final containers should be kept continuously at a temperature that minimizes potency loss (for example, in the frozen state at a temperature below −20 °C).

To facilitate vaccine distribution, OPV may be stored at a higher temperature for a specified period during shipping and distribution in the field – for example, at 2–8 °C for 6 months. In addition, during manufacturing, shipping or in the field, the vaccine may be thawed and refrozen. Manufacturers should conduct real-time and real-condition stability studies to support the storage conditions at different temperatures as well as the maximum permitted number of freeze–thaw cycles. The stability data should demonstrate that the vaccine conforms to the requirements of potency until the expiry date stated on the label, as approved by the NRA.

A.11.3 Expiry date

The expiry date should be based on the shelf-life as supported by the stability studies and approved by the NRA. The start of the dating period should be specified (for example, based on the date of filling or the date of the first valid potency test on the final lot) and should be approved by the NRA.

Part B. Nonclinical evaluation of poliomyelitis vaccines (oral, live, attenuated)

The nonclinical evaluation of candidate poliomyelitis vaccines (oral, live, attenuated) should be based on the principles outlined in the WHO guidelines on nonclinical evaluation of vaccines (20) which provide guidance on the design, conduct, analysis and evaluation of nonclinical studies. In addition, all changes made to a product post-approval should follow the requirements listed in the WHO Guidelines on procedures and data requirements for changes to approved
vaccines (68). The following specific issues should be considered in addition to the tests described above in section A.3.2.3 following a change in the virus seed.

B.1 **Characterization of a new Sabin virus sub-master seed**

In the event that a new Sabin virus sub-master seed is prepared by a single passage from a well-characterized master seed (including the WHO master seed) it should be subjected to extensive characterization. This should include evaluation of at least one virus working seed and three monovalent bulks derived from it, as described in section A.4.4.7 above. Characterization studies must include the evaluation of identity by complete nucleotide sequencing to prove that the new sub-master seed consensus sequence is identical to conventional Sabin master seeds and that the mutational composition (for example, in MAPREC) is consistent. HTS should be undertaken to evaluate the heterogeneity of the virus sequence. These approaches have not yet been formally validated with the exception of the MAPREC assays for base positions in the 5’ UTR of type 3 OPV, as described in section A.4.4.7.1 above. A new virus sub-master seed should be tested for neurovirulence using the MNVT or TgmNVT, subject to the approval of the NRA. Summaries of the MNVT and TgmNVT are provided below in Appendix 2, along with considerations in the choice of assay.

B.2 **Characterization of virus seeds for the production of nOPV**

Virus strains used for the production of nOPV were constructed using recombinant DNA technology and are genetically stabilized attenuated strains designed based on current knowledge of the molecular mechanisms of attenuation and reversion of poliovirus. The virus master, sub-master (if applicable) and working seed lots used to manufacture a candidate nOPV should be subjected to extensive characterization. This should include evaluation of at least three monovalent bulks derived from the working seed, as described in section A.4.4.7 above. In addition, the genetic stability of the strains used for nOPV production should be confirmed at least at the passage level (or beyond) used to prepare the vaccine, and using a molecular method approved by the NRA, such as whole-genome HTS analysis.

B.3 **Evaluation of immunogenicity of nOPV in suitable models**

The genomes of nOPV production strains are rationally designed to stabilize attenuation. However, variations can arise in the viral genomes of nOPV production strains on passage in cell cultures. Whether these genome changes (introduced or cumulated) have any impact on the immunogenicity of the candidate nOPV should be studied using suitable methods – for example, evaluation of the antigenicity of the production strain and/or its ability to
grow in in vitro cell culture. If required, based on the outcomes of the in vitro testing, transgenic mice with interferon-receptor knock-out and expression of human poliovirus receptor are available to study vaccine-induced neutralizing antibodies. Proof-of-concept nonclinical studies based on type-specific serum neutralizing antibody titres may also assist in the selection of the doses to be tested in the clinical dose-finding studies.

Part C. Clinical evaluation of poliomyelitis vaccines (oral, live, attenuated)

Clinical trials should adhere to the principles described in the WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products (69) and WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (21). All clinical trials should be approved by the relevant NRAs.

A number of issues specific to the clinical evaluation of OPV are discussed in the following sections, which should be read in conjunction with the general guidance mentioned above. It is also recommended that manufacturers should consult with the relevant NRAs regarding the overall clinical development programme.

The following sections consider the provision of clinical data required for:

- nOPV prepared from genetically stabilized attenuated strains;
- new formulations based on licensed OPVs that are derived from Sabin poliovirus strains, including monovalent, bivalent and trivalent vaccines; and
- situations in which major changes have been made to the manufacturing process of an established vaccine (for example, changing from primary monkey kidney cells to a cell line).

Clinical evaluation is not required for a vaccine manufactured using a new virus working seed lot, provided that the passage level is not more than one from the master/sub-master seed lot, the working seed has been characterized and the consistency of the manufacturing process demonstrated (see sections A.3.2.3 above). Generating a new sub-master seed lot requires extensive characterization but not clinical trials (see Part B above).

Vaccine formulations containing one or two poliovirus serotypes have been licensed based on clinical trials in endemic countries. The results of clinical trials in Egypt and northern India indicated that the efficacy of mOPV1 was superior to that of tOPV in terms of inducing immunity against poliovirus type 1 (35, 70). Health authorities therefore recommended the widespread use of mOPV1 to eliminate poliovirus type 1 transmission in India. In addition, studies
of bOPV containing type 1 and type 3 demonstrated that it was non inferior to mOPV1 and mOPV3 individually, and superior to tOPV against poliovirus type 1 and type 3 (71).

C.1 General considerations
Prompted by World Health Assembly resolution WHA41.28 in 1988, the GPEI has led to a dramatic decrease in poliomyelitis cases globally (27). As a result, efficacy studies for poliomyelitis vaccines are not feasible, and clinical evaluations and seroprevalence studies should therefore compare the safety and immunogenicity of candidate vaccines against a licensed (comparator) vaccine. The assessment of seroconversion should be based on the elicitation of neutralizing antibodies, which are the basis of protection (27). The approval of a candidate OPV should be based on a clear demonstration of non-inferiority compared with a licensed OPV or an OPV used under WHO EUL, as described below in section C.2.2. The relative risk of VAPP for a new candidate vaccine versus approved vaccines cannot be estimated from pre-approval studies but should be addressed as part of post-marketing surveillance. In addition, the genetic stability of any nOPV strain should be verified during clinical studies.

C.2 Immunogenicity and safety studies
C.2.1 Assessment of the immune response
The presence of neutralizing antibodies against polioviruses is considered a reliable correlate of protection against poliomyelitis. However, immunity induced by one serotype does not provide protection against the other two serotypes. A serum neutralizing antibody titre of \( \geq 8 \) is considered to be a marker of clinical protection against poliomyelitis (72). The demonstration of an immune response to OPV administration should be based on the measurement of neutralizing antibody titres at pre- and post-vaccination time points. Seroconversion for poliovirus antigen is defined as:

- for subjects seronegative at the pre-vaccination time point, post-vaccination antibody titres of \( \geq 8 \);
- for subjects seropositive at the pre-vaccination time point, a four-fold or greater rise in post-vaccination antibody titres. If the pre-vaccination titre is due to maternal antibodies, a four-fold rise above the expected titre of maternal antibodies based on the pre-vaccination titre declining with a half-life of 28 days indicates seroconversion, or post-vaccination antibody titres of \( \geq 8 \), whichever is higher.

The assay used to assess serum neutralizing antibodies in the clinical samples should follow the key parameters described in the WHO Manual for the
virological investigation of poliomyelitis (73), with the exception of the challenge poliovirus strains. OPV developers are instead encouraged to use genetically modified poliovirus strains that can be manipulated outside of containment facilities (for example, S19 strains) as challenge viruses. The level of neutralizing antibody present in a serum sample is expressed as a titre, which is the reciprocal of the highest serum dilution that inhibits the viral cytopathic effect in 50% of cell cultures. A reference serum calibrated against, or traceable to, the appropriate WHO international standard (see Appendix 8) should be used to control assay performance.

Geometric mean titres, seroconversion rates and reverse cumulative distributions should be provided.

C.2.2 Immunogenicity studies

New candidate OPVs manufactured from genetically stabilized attenuated strains or using different vaccine compositions (monovalent, bivalent or trivalent) should be compared with a licensed OPV or an OPV used under WHO EUL. The comparator vaccine(s) selected should have been in use for several years so that data on their effectiveness are available, in addition to a reliable description of their safety profile. When no licensed type-matched OPV is available for use in clinical trials, one or more licensed OPV (or nOPV used under WHO EUL) may be used as the comparator(s) to cover all serotypes included in the candidate vaccine. For example, a candidate tOPV prepared from genetically stabilized attenuated strains may be compared to two suitable comparators – one bivalent and the other monovalent – in a non-inferiority immunogenicity study. In this case, any potential impact on immunogenicity outcomes (for example, a negative immune interference) due to different compositions/serotypes between the comparators and candidate vaccines should be considered in the study design. Further guidance on the selection of comparators is provided in the WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (21). In all cases, the study design should be discussed with and approved by the NRA.

C.2.3 Population

The immunogenicity data provided to support the licensure of a candidate OPV as a primary series should include data generated in a naive target population, such as infants. The evaluation of new OPV formulations prepared from Sabin strains may be conducted directly in infants and newborns since safety profiles in these populations have already been established. However, the first clinical study (Phase I) of a candidate nOPV should be performed in healthy adults to assess vaccine safety.

The study exclusion criteria should reflect the current contraindications to administration of OPVs.
C.2.4 **End-points and analyses**

The clinical study protocol should state the primary objective(s) of the study. The neutralizing antibody response to the candidate vaccine should be demonstrated to be non-inferior versus an appropriate licensed OPV or an OPV used under WHO EUL, as described in C.2.2 above, based primarily on geometric mean titres and/or seroconversion rates. The primary end-point should be selected according to the study population and the anticipated immune response. For example, very high seroprevalence rates are expected in highly immunized populations, with implications for the selection of the non-inferiority margin and therefore the sample size calculation. Further guidance on demonstrating non-inferiority is provided in the WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (21).

Other immunological parameters should be compared in planned secondary analyses (for example, percentages reaching predefined titres).

C.2.5 **Dose-ranging studies**

At the time of publication of this document, all licensed Sabin OPV formulations (monovalent, bivalent and trivalent) contained the recommended dose for each poliovirus type (not less than $10^{6.0}$ CCID$_{50}$ for type 1, $10^{5.0}$ CCID$_{50}$ for type 2 and $10^{5.5}$ CCID$_{50}$ for type 3). However, the development of nOPV or novel formulations with improved stability (through the addition of stabilizers/exipients) or improved immunogenicity (through the use of an adjuvant) may require dose-ranging studies to determine the minimum dose of virus required in CCID$_{50}$ to provide adequate immune responses (21). These data could also be used to support the minimum viral titre that should be present in the vaccine at the end of its shelf-life.

C.2.6 **Vaccine virus shedding and transmission**

Changes in the viral genome of candidate nOPVs, or changes in vaccine composition, may impact virus replication in the intestinal tract and may influence the ability of the vaccine to induce immune responses, with the potential for VAPP or the spread of vaccine viruses to non-target populations. Manufacturers should undertake studies to determine the profile of the vaccine virus (if applicable, by serotype) excreted in the stools of vaccinees, and the duration of shedding. The excretion of candidate nOPV viruses or viruses used in new vaccine formulations should be evaluated alongside a licensed OPV product or an OPV product used under WHO EUL (35). For nOPV, virus recovered from stool samples collected from the vaccinees should be evaluated by HTS to verify the genetic stability of the candidate vaccine virus. Genome regions that include key attenuating mutations should be examined, and any genetic variations in the whole genome monitored.
C.2.7 Challenge studies with attenuated Sabin poliovirus

Induction of mucosal immunity by the candidate and comparator vaccines should be determined by the assessment of virus excretion following the administration of a challenge dose of OPV, such as nOPV. Excretion of poliovirus in stool specimens is determined at various intervals immediately before the challenge (day 0) and on days 7, 14, 21 and 28 thereafter (70).

C.2.8 Concomitant administration with other vaccines

An evaluation of the effects of co-administration of an OPV with other vaccines should be considered, taking into account which vaccines are most likely to be given concomitantly in different age groups and populations.

When OPVs are used in an EPI programme simultaneously with other vaccines, it is particularly important that the effects of co-administration are evaluated (for example, in co-administration studies with rotavirus vaccines which are also administered via the oral route).

Immune responses to all other antigens co-administered with the new OPV should be measured at least in subsets. While the study will usually be powered only to demonstrate non-inferiority with respect to neutralizing antibody against the different poliovirus types used in the vaccine, the protocols should at least include planned secondary analyses of antigen-specific responses. If these analyses indicate that immune responses are lower on co-administration with a new OPV compared to the licensed vaccine(s), NRAs will need to consider the potential clinical consequences on a case-by-case basis.

C.2.9 Pre-licensure safety data

The general approach taken to assess the safety of a new OPV during clinical studies should be in accordance with the WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (21). Planned safety studies should be supported by a clear scientific rationale. Given the long history of the use of vaccines based on Sabin strains, the NRA may decide that additional pre-licensure safety studies are not required. When a new vaccine formulation that has not previously been used is being investigated, larger-scale studies will be needed.

An appropriate pharmacovigilance plan should be developed, and should be approved by the NRA prior to licensure.

C.3 Post-marketing studies and surveillance

Enhanced safety surveillance, particularly for the detection of VAPP, should be undertaken during the initial post-approval years in collaboration with NRAs. Environmental surveillance should also be conducted. The benefits and risks of using mOPV and bOPV derived from Sabin strains should be carefully
considered, as in areas with sub-optimal polio vaccine coverage this may lead to the emergence of cVDPVs. Manufacturers and health authorities should work in collaboration with the global polio surveillance laboratory network19 to monitor new vaccines once they are introduced into immunization programmes. These laboratories have extensive experience in poliovirus surveillance and can provide excellent surveillance and post-marketing support.

The total duration of enhanced surveillance should be regularly reviewed by the NRA. If particular issues arise during pre-licensure studies or during post-licensure safety surveillance, it may be necessary to conduct specific post-licensure safety studies.

Part D. Recommendations for NRAs

D.1 General recommendations

The guidance for NRAs and NCLs given in the WHO Guidelines for national authorities on quality assurance for biological products (74) and WHO Guidelines for independent lot release of vaccines by regulatory authorities (24) should be followed. These guidelines specify that no new biological product should be released until consistency of manufacturing and product quality have been established and demonstrated by the manufacturer.

The detailed production and control procedures, as well as any significant changes in them that may affect the quality, safety and efficacy of live attenuated OPV should be discussed with and approved by the NRA.

For control purposes, the relevant international reference materials currently in force should be obtained for the purpose of calibrating national, regional and working standards as appropriate (75). The NRA may obtain the product-specific or working reference from the manufacturer to be used for lot release until the international/national standard is established.

Only a monovalent bulk approved by the NRA can be used by the manufacturer for the formulation of a final bulk.

Where the MNVT is performed for the control of the monovalent bulk and the NCL does not perform this test itself, the NCL should carry out a second evaluation of the histological sections provided by the manufacturer for each monovalent bulk. In addition, the NCL or a contract organization certified by the NRA for proficiency in conducting NVTs should perform a second evaluation of the results of at least four MNVTs on the reference preparations to obtain the necessary baseline data for comparison with the neurovirulence of the test

vaccines. The NCL should encourage the use of a standard form for the reporting of data on virus activity in the sections taken for histopathological examination.

Where the TgmNVT is performed for the control of the monovalent bulk and the NCL performs this test itself, the standard implementation process should be followed. If the NCL does not perform the test, it should carry out a clinical scoring of mice in parallel with the manufacturer at least at day 3 or day 4. Only appropriately trained staff from a competent NCL can carry out a clinical scoring of mice in parallel with the manufacturer. Whether or not a clinical scoring at day 14 is needed should be justified for each monovalent bulk. Moreover, once a year, the injection of mice should be observed by the NCL.

In one region of the world, 1 in 10 bulks are also independently tested by an NCL competent in carrying out the test. Other regions that implement the TgmNVT may wish to follow this approach.

Consistency of production has been recognized as an essential component in the quality assurance of live attenuated OPV. In particular, the NRA should carefully monitor production records and quality control test results for clinical lots, as well as for a series of consecutive lots of the vaccine.

D.2 Official release and certification

A vaccine lot should be released only if it fulfils all national requirements and/or satisfies Part A of these WHO Recommendations (24).

A summary protocol for the manufacturing and control of OPV, based on the model summary protocol provided below in Appendix 5 and signed by the responsible official of the manufacturing establishment, should be prepared and submitted to the NRA/NCL in support of a request for the release of the vaccine for use.

A lot release certificate signed by the appropriate NRA/NCL official should then be provided if requested by the manufacturing establishment, and should certify that the lot of vaccine meets all national requirements and/or Part A of these WHO Recommendations. The certificate should provide sufficient information on the vaccine lot, including the basis of the release decision (by summary protocol review and/or independent laboratory testing). The purpose of this official national lot release certificate is to facilitate the exchange of vaccines between countries, and should be provided to importers of the vaccines.

A model NRA/NCL Lot Release Certificate for poliomyelitis vaccines (oral, live, attenuated) is provided below in Appendix 6.
Part E. Recommendations for poliomyelitis vaccines (oral, live, attenuated) prepared in primary monkey kidney cells

The following additional or alternative recommendations are for Sabin OPV prepared in cultures of primary monkey kidney cells and concern the testing of the cell substrate used for the production of the vaccine. They should therefore be either added to or used as an alternative to the appropriate sections of section A.4 above as follows:

- sections E.1.1.1, E.1.3.1, E.1.4.1 and E.1.4.2 are additions to the corresponding section A.4 text (as individually indicated below); and
- sections E.1.2.1–E.1.2.3 are replacements for the corresponding section A.4 text (as individually indicated below).

All other recommendations given in Parts A and B of this document are also applicable to this type of vaccine.

E.1 Control of vaccine production

E.1.1 Control of source materials

E.1.1.1 Monkeys used for the preparation of kidney cell cultures and testing of virus
[Addition to section A.4.1]

If vaccine is prepared in monkey kidney cell cultures, the animals should be from a species approved by the NRA, and should be in good health and not previously have been used for experimental purposes.

Manufacturers should use animals from closed or intensively monitored colonies.

The monkeys should be kept in well-constructed and adequately ventilated animal rooms in cages separated in such a way as to prevent cross-infection between cages. Cage mates should not be interchanged. The monkeys should be kept in the country of manufacture of the vaccine in quarantine groups\(^{20}\) for a period of not less than 6 weeks before use. If at any time during the quarantine period the overall death rate of a shipment consisting of one or more groups reaches 5% (excluding deaths from accidents or where the cause was specifically determined not to be an infectious disease), all the monkeys from that entire shipment should continue to be quarantined for a further period of

\(^{20}\) A quarantine group is a colony of selected healthy monkeys kept in one room, with separated feeding and cleaning facilities, and having no contact with other monkeys during the quarantine period.
not less than 6 weeks. The monkeys used should be free of infection. At the end of the extended quarantine period, and following thorough investigations, if any additional monkeys die of the same infectious disease, the entire group is to be discarded from production.

The groups should be kept continuously in isolation, as in quarantine, even after completion of the quarantine period, until the monkeys are used. After the last monkey of a group has been taken, the room that housed the group should be thoroughly cleaned and decontaminated before being used for a fresh group.

In countries in which the kidneys from near-term monkeys are used, the mother should be quarantined for the term of the pregnancy.

All actions taken by working personnel should be based on the assumption that a great potential hazard exists at all times in the quarantine area. Personnel should be provided with protective clothing, including gloves, footwear and masks or visors. Street clothes should not be permitted in the animal rooms. Smoking, eating and drinking should be forbidden while personnel are in the animal rooms.

A supervisor should be made responsible for reporting any unusual illness among employees and for ensuring that all injuries are properly treated. No worker who has cuts or abrasions on exposed areas of the body should enter the animal area. Any unexplained febrile illness, even while off duty, should be considered as potentially related to the employee's occupation.

Monkeys from which kidneys are to be removed should be anaesthetized and thoroughly examined, particularly for evidence of tuberculosis and herpes B virus infection.

If a monkey shows any pathological lesion relevant to the use of its kidneys in the preparation of a seed lot or vaccine, it should not be used, and nor should any of the remaining monkeys of the same quarantine group be used unless it is evident that their use will not impair the safety of the product.

All the operations described in this section should be conducted outside the areas where vaccine is made.

The monkeys should be shown to be free from antibodies to SV40 and simian immunodeficiency virus.

It is desirable that kidney cell cultures are derived from monkeys shown to be free from antibodies to foamy viruses. In some countries, monkeys are tested for antibodies to herpes B virus.

E.1.2 Production precautions

The general production precautions called for in WHO good manufacturing practices for biological products (22) should apply to the manufacture of the vaccine, with the addition of the following tests.
E.1.2.1  Monkey kidney cell cultures for vaccine production

[Replacement of section A.4.2.1 above – in conjunction with section E.1.2.2 below]

Cultures of monkey kidney cells should be prepared from kidneys that have shown no pathological signs. Virus for the preparation of vaccine should be grown by aseptic methods in such cultures. If animal serum is used in the propagation of the cells, the maintenance medium used after virus inoculation should contain no added serum.

To reduce animal use, the virus may be grown in serially passaged monkey kidney cell cultures derived from primary monkey kidney cells.

Each group of cell cultures derived from a single monkey, or from no more than 10 near-term monkeys, should be prepared and tested as an individual group.

E.1.2.2  Tests of cell cultures used for vaccine production (see Appendix 7)

[Replacement of section A.4.2.1 above – in conjunction with section E.1.2.1 above]

On the day of inoculation with the virus working seed lot, each cell culture should be examined for degeneration caused by an infective agent. If, during this examination, evidence is found of the presence in a cell culture of any adventitious agent, the entire group of cultures concerned should not be used for vaccine production.

On the day of inoculation with the virus working seed lot, a sample of at least 30 mL of the pooled fluid removed from the cell cultures of the kidneys of each single monkey, or from no more than 10 near-term monkeys, should be divided into two equal portions. One portion of the pooled fluid should be tested in monkey kidney cell cultures prepared from the same species (but not the same animal) as that used for vaccine production. The other portion of the pooled fluid should be tested in kidney cell cultures from another species of monkey, provided that the tests are done in cell cultures from at least one species known to be sensitive to SV40. The pooled fluid should be inoculated into bottles of these cell cultures in such a way that the dilution of the pooled fluid in the nutrient medium does not exceed 1 part in 4. The area of the cell sheet should be at least 3 cm² per mL of pooled fluid. At least one bottle of each kind of cell culture should remain uninoculated and should serve as a control.

When the monkey species used for vaccine production is known to be sensitive to SV40, a test in a second species may be omitted with the approval of the NRA.
Animal serum may be used in the propagation of the cells provided that it does not contain SV40 antibody or other inhibitors, but the maintenance medium used after inoculation of the test material should contain no added serum except as described below.

The cultures should be incubated at a temperature of 35–37 °C and should be observed for a total period of at least 4 weeks. During this observation period, and after not less than 2 weeks of incubation, at least one subculture of fluid should be made from each of the cultures in the same tissue culture system. The subculture should also be observed for at least 2 weeks.

Serum may be added to the original culture at the time of subculturing provided that the serum does not contain SV40 antibody or other inhibitors. Immunochemical techniques may be useful for detecting SV40 and other viruses in the cells.

A further sample of at least 10 mL of the pooled fluid should be tested for the presence of herpes B virus and other viruses in rabbit kidney cell cultures. Serum used in the nutrient medium of these cultures should have been shown to be free from inhibitors. The sample should be inoculated into bottles of these cell cultures in such a way that the dilution of the pooled fluid in the nutrient medium does not exceed 1 part in 4. The area of the cell sheet should be at least 3 cm² per mL of pooled fluid. At least one bottle of the cell cultures should remain uninoculated and should serve as a control.

The cultures should be incubated at a temperature of 35–37 °C and should be observed for at least 2 weeks.

It is suggested that, in addition to these tests, a further sample of 10 mL of pooled fluid removed from the cell cultures on the day of inoculation with the seed lot virus should be tested for the presence of adventitious agents by inoculation into cell cultures sensitive to measles virus.

For the tests to be valid, not more than 20% of the culture vessels should have been discarded for any reason by the end of the respective test periods.

If, during these tests, evidence is found of the presence of an adventitious agent, the single harvest from the whole group of cell cultures concerned should not be used for vaccine production.

If the presence of the herpes B virus is demonstrated, vaccine manufacture should be discontinued and the NRA informed. Manufacturing should not be resumed until a thorough investigation has been completed and precautions have been taken against any reappearance of the infection, and then only with the approval of the NRA.

---

21 Human herpesvirus (herpes simplex) has been used as an indicator of freedom from B virus inhibitors because of the danger of handling herpes B virus.
If these tests are not carried out immediately, the samples of pooled cell culture fluid should be kept at a temperature of −60 °C or below, with the exception of the sample to be used for the test for herpes B virus, which may be held at 4 °C provided that the test is done not more than 7 days after the sample has been taken.

E.1.2.3 Test of control cell cultures

[Replacement of section A.4.1 above]

Cultures prepared on the day of inoculation with the virus working seed lot from 25% (but not more than 2.5 L) of the cell suspension obtained from the kidneys of each single monkey, or from not more than 10 near-term monkeys, should remain uninoculated and should serve as controls. These control cell cultures should be incubated under the same conditions as the inoculated cultures for at least 2 weeks, and should be examined during this period for evidence of cytopathic changes. For the tests to be valid, not more than 20% of the control cell cultures should have been discarded for any reason. At the end of the observation period, the control cell cultures should be examined for degeneration caused by an infectious agent. If this examination, or any of the tests required in this section, show evidence of the presence of any adventitious agent in a control culture, the poliovirus grown in the corresponding inoculated cultures from the same group should not be used for vaccine production.

E.1.2.3.1 Tests for haemadsorbing viruses

At the time of harvest, or not more than 4 days after the day of inoculation of the production cultures with the virus working seed lot, a sample of 4% of the control cell cultures should be taken and should be tested for haemadsorbing viruses. At the end of the observation period, the remaining control cell cultures should be similarly tested. The tests should be carried out as described above in section A.4.1.2.

E.1.2.3.2 Tests for other adventitious agents

At the time of harvest, or no more than 7 days after the day of inoculation of the production cultures with the virus working seed lot, a sample of at least 20 mL of the pooled fluid from each group of control cultures should be taken and tested in two kinds of monkey kidney cell culture, as described in section E.1.2.2 above.

At the end of the observation period for the original control cell cultures, similar samples of the pooled fluid should be taken and the tests referred to in this section in the two kinds of monkey kidney cell culture and in the rabbit cell culture should be repeated, as described in section E.1.2.2 above.
If the presence of herpes B virus is demonstrated, the production cell cultures should not be used and the measures concerning vaccine production described above in section E.1.2.2 should be taken.

In some countries, fluids are collected from the control cell cultures at the time of virus harvest and at the end of the observation period. Such fluids may then be pooled before testing for adventitious agents.

E.1.3 **Control of single harvests**

[Addition to section A.4.3 above]

E.1.3.1 **Tests for neutralized single harvests in monkey kidney cell cultures**

A sample of at least 10 mL of each single harvest should be neutralized by type-specific poliovirus antiserum prepared in animals other than monkeys. In preparing antisera for this purpose, the immunizing antigens used should be prepared in non-simian cells.

Care should be taken to ensure that the antiserum used is monospecific. This may be demonstrated by titration of the antiserum against homotypic and heterotypic viruses of known virus titre using the same dilution of the antiserum as that used for neutralization.

Half (corresponding to at least 5 mL of single harvest) of the neutralized suspension should be tested in monkey kidney cell cultures prepared from the same species (but not the same animal) as that used for vaccine production. The other half of the neutralized suspension should be tested in monkey kidney cell cultures from another species, provided that the tests are done in cell cultures from at least one species known to be sensitive to SV40.

The neutralized suspensions should be inoculated into bottles of these cell cultures in such a way that the dilution of the suspension in the nutrient medium does not exceed 1 part in 4. The area of the cell sheet should be at least 3 cm² per mL of neutralized suspension. At least one bottle of each kind of cell culture should remain uninoculated to serve as a control and should be maintained using nutrient medium containing the same concentration of the specific antiserum used for neutralization.

Animal serum may be used in the propagation of the cells provided that it does not contain inhibitors, but the maintenance medium used after the inoculation of the test material should contain no added serum other than the poliovirus neutralizing antiserum, except as described below.

The cultures should be incubated at a temperature of 35–37 °C and should be observed for a total period of at least 4 weeks. During this observation period, and after no less than 2 weeks of incubation, at least one subculture
of fluid should be made from each of these cultures in the same tissue culture system. The subcultures should also be observed for at least 2 weeks.

Serum may be added to the original cultures at the time of subculturing provided that the serum does not contain inhibitors. Immunohistochemical techniques may be useful for detecting SV40 and other viruses in the cells.

It is suggested that, in addition to these tests, a further sample of the neutralized single harvest is tested by inoculation of 10 mL into human cell cultures sensitive to measles virus.

For the tests to be valid, not more than 20% of the culture vessels should have been discarded for any reason by the end of the respective test periods.

If any cytopathic changes occur in any of the cultures, the causes of these changes should be investigated. If the cytopathic changes are shown to be due to un-neutralized poliovirus, the test should be repeated. If there is evidence of the presence of SV40 or other adventitious agents attributable to the single harvest, that single harvest should not be used for vaccine production.

E.1.4 Control of monovalent bulk
[Addition to section A.4 above]

E.1.4.1 Monovalent bulk (before filtration)
E.1.4.1.1 Tests in rabbits

A sample of the monovalent bulk should be tested for the presence of herpes B virus and other viruses by injection into at least 10 healthy rabbits each weighing between 1.5 and 2.5 kg. The total sample volume should be at least 100 mL. Each rabbit should receive not less than 10 mL and not more than 20 mL – of which 1 mL should be administered intradermally at multiple sites and the remainder subcutaneously. The rabbits should be observed for between 3 and 5 weeks for death or signs of illness.

It is suggested that the sample should consist of at least 1% of the total monovalent bulk (provided that this is not less than 100 mL) up to a maximum of 500 mL.

All rabbits that die during the testing period should be examined by autopsy, with the brain and other organs being removed for detailed examination to establish the cause of death. Animals showing signs of illness should be humanely killed and subjected to a similar autopsy.

The monovalent bulk passes the test if no more than 20% of the inoculated rabbits show signs of infection during the observation period and
if none of the rabbits show evidence of infection with herpes B virus or other adventitious agents, or lesions of any kind attributable to the bulk suspension.

If the presence of herpes B virus is demonstrated, then the measures concerning vaccine production described above in section E.1.2.2 should be taken.

A test for the presence of Marburg virus may be carried out in guinea-pigs.

E.1.4.2 Monovalent bulk (after filtration) – tests for retroviruses

Test samples from the filtered monovalent bulk should be examined for the presence of retroviruses using an assay for reverse transcriptase acceptable to the NRA.

Authors and acknowledgements

The first draft of these WHO Recommendations was prepared by a WHO drafting group comprising Dr K. Chumakov, United States Food and Drug Administration, the USA; Dr C. Li, National Institutes for Food and Drug Control, China; Dr L. Mallet, European Directorate for the Quality of Medicines & HealthCare, France; Dr J. Martin, Medicines and Healthcare products Regulatory Agency, the United Kingdom; Dr T. Wu, Health Canada, Canada; and Dr T.Q. Zhou, World Health Organization, Switzerland. Acknowledgement is also due to Dr P. Minor, St Albans, the United Kingdom for his critical review and valuable input.

The first draft was then reviewed at a WHO informal consultation on the revision of recommendations to assure the quality, safety and efficacy of oral poliomyelitis vaccines, held virtually on 15–17 November 2021, and attended by: Miss P. Agsiri, Ministry of Public Health, Thailand; Dr L.R. Andalucia, Indonesian Food and Drug Authority, Indonesia; Dr M. Arita, National Institute of Infectious Diseases, Japan; Dr A. Bhardwaj, Central Drugs Standard Control Organisation, India; Mr R.M. Bretas, Agência Nacional de Vigilância Sanitária, Brazil; Dr M. Bruysters, National Institute for Public Health and the Environment, Netherlands; Dr K. Chumakov, United States Food and Drug Administration, the USA; Ms G. Cooper, Medicines and Healthcare products Regulatory Agency, the United Kingdom; Dr V. Dhawan, Ministry of Health and Family Welfare, India; Dr S. Fakhrzadeh, Ministry of Health and Medical Education, the Islamic Republic of Iran; Dr E. Grabski, Paul-Ehrlich-Institut, Germany; Dr N. Gupta, Ministry of Health and Family Welfare, India; Dr P. Haldar, Government of India, India; Mrs T. Jivapaisarnpong, King Mongkut’s University of Technology Thonburi, Thailand; Dr J. Konz, PATH, the USA; Dr C. Li, National Institutes for Food and Drug Control, China; Dr K. Mahmood, PATH, the USA; Dr M.
Majumdar, Medicines and Healthcare products Regulatory Agency, the United Kingdom; Dr L. Mallet, European Directorate for the Quality of Medicines & HealthCare, France; Dr J. Martin, Medicines and Healthcare products Regulatory Agency, the United Kingdom; Dr C. Milne, European Directorate for the Quality of Medicines & Healthcare, France; Dr P. Minor, St Albans, the United Kingdom; Sr Si Normasari, Indonesian Food and Drug Authority, Indonesia; Dr V. Pithon, Agence nationale de sécurité du medicament et des produits de sante, France; Dr D.E. Putri, Indonesian Food and Drug Authority, Indonesia; Dr S.E. Reddy, Central Drugs Standard Control Organisation, India; Dr L. Stephens, Medicines and Healthcare products Regulatory Agency, the United Kingdom; Dr A. Macadam, Medicines and Healthcare products Regulatory Agency, the United Kingdom; Dr S. Pumiamorn, Ministry of Public Health, Thailand; Dr G. Waeterloos, Sciensano, Belgium; and Dr T. Wu, Health Canada, Canada.

Representatives of the Developing Countries Vaccine Manufacturers Network: Dr R. Cuber, Bio-Manguinhos, Brazil; Dr R. Dhere, Serum Institute of India, India; Ms T.T.B. Hanh, Polyvac, Viet Nam; Mr W. Hidayat, BioFarma, Indonesia; Mr L.Q. Hung, Polyvac, Viet Nam; Dr M. Jain, Panacea Biotec, India; Mr S. Kosaraju, Biological E, India; Dr Y. Li, Institute of Medical Biology, Chinese Academy of Medical Sciences, China; Dr K. Maithal, Zydus-Cadila Healthcare Ltd, India; Dr S.B. Rajan, Zydus-Cadila Healthcare Ltd, India; Mr M.I. Masud, Incepta Vaccine Ltd, Bangladesh; Dr L. Mohanty, Panacea Biotec, India; Mr P. Morgon, Cansino Bio, China; Ms L.T. Nga, Polyvac, Viet Nam; Mr P. Pavuluri, Biological E, India; Mr V. Sivaramakrishnan, Bharat Biotech International, India; Dr V.K. Srinivas, Bharat Biotech International, India; Mr M. Stetsyuk, Nanolek, Russian Federation; Ms J. Tresnabudi, BioFarma, Indonesia; Mr D. Ugiyadi, BioFarma, Indonesia; Dr X.L. Yang, Institute of Medical Biology, Chinese Academy of Medical Sciences, China; Dr Y.C. Zhang, Beijing Institute of Biological Products Co., Ltd, China. Individual manufacturers: Dr A. Stefanovic, Bilthoven Biologicals, Netherlands; Dr A. Malkin and Dr A. Sinyagina, Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products of the Russian Academy of Sciences, Russian Federation. WHO Secretariat: Dr T.Q. Zhou and Dr I. Knezevic, Health Products Policy and Standards Department, World Health Organization, Switzerland.

Based on the outcomes of the above informal consultation, a second draft was prepared by the above WHO drafting group with input from Dr P. Minor, St Albans, the United Kingdom. The resulting document was then posted on the WHO Biologicals website during February and March 2022 for a first round of public consultation. Feedback and comments were received from: Dr J. Konz, Dr C. Gast and Dr M. Toher, PATH, the USA; Dr M. Ergasheva, Ministry of Health of the Republic of Uzbekistan, Uzbekistan; Dr R-C Guimarães, Bio-
Manguinhos/Fiocruz; Dr I. Fradi, Ministry of Health, Tunisia; Dr C. Milne, European Directorate for the Quality of Medicines & Healthcare, France; Dr V. Pithon, Agence nationale de sécurité du médicament et des produits de santé, France; Dr D. Das and Dr F. Atouf, United States Pharmacopeia, the USA; Dr A.E. de Almeida, Oswaldo Cruz Foundation, Brazil; and Dr A. Malkin, Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products of the Russian Academy of Sciences, Russian Federation.

Taking into consideration the comments received, the document WHO/BS/2022.2423 was prepared by the above WHO drafting group and then posted on the WHO Biologicals website for a second round of public consultation during June and August 2022. Written comments were received from: Ms Y. Chen, Beijing Institute of Biological Products Co. Ltd, China; Dr S. Wendel, Hospital Sírio-Libanês Blood Bank, Brazil; Dr B. Zhao, Institute of Medical Biology, Chinese Academy of Medical Sciences, China; Dr A. Muhaidat and Dr M. Malkawy, Jordan Food and Drug Administration, Jordan; Dr A.K. Tahlan, Central Research Institute, India; and Dr M. Mamdouh and Dr A. Fouad, Egyptian Drug Authority, Egypt.

Further changes were made to document WHO/BS/2022.2423 by the WHO Expert Committee on Biological Standardization.

References


Appendix 1

Overview of virus seeds used in OPV production

The history of the poliovirus strains used in the production of OPV is well documented (1–3). This appendix provides an overview of virus seeds used in OPV production.

Fig. 2.1 and Fig. 2.2 show the histories of seed virus and reference materials used in the manufacture of OPV from Sabin 1 and Sabin 2 (Fig. 1) and Sabin 3 (Fig. 2). Concentric circles indicate progressive virus passages made to prepare master seed stocks, working seed stocks and production lots of vaccine. Where relevant, sub-master seed stocks are identified in the notes. Different seed viruses are identified as SO (Sabin Original), SOM (Sabin Original Merck), SOB (Sabin Original Behringwerke), RSO (otherwise known as Pfizer strain), SOJ (Sabin Original Japanese) and SOR (Sabin Original Russian).

Fig. 2.1
Types 1 and 2 OPV produced from Sabin 1 and Sabin 2
These figures provide only a historical overview of the use of different seeds derived from the Sabin vaccine strain in OPV production. They do not imply any WHO “qualification” or “approval” of the strains or vaccines in the context of this document.

The origin of the nOPV given emergency use listing (EUL) by WHO in 2020 has been published (4) but this has not yet been provided as a seed by WHO. The design and purpose of the modifications are described in Fig. 3.

Fig. 2.2
Type 3 OPV produced from Sabin 3

The manufacturers corresponding to the countries shown in Fig. 2.1 and Fig. 2.2 are:

Belgium: GlaxoSmithKline Biologicals
China (1): Institute of Medical Biology, Chinese Academy of Medical Sciences

China (2):
China (2) China National Biotec Group, Beijing Tiantan Biological Products Company
France Sanofi Aventis
Indonesia PT Bio Farma
Islamic Republic of Iran Razi Vaccine and Serum Research Institute
Italy Novartis Vaccines
Japan Japan Poliomyelitis Research Institute (JPRI)
Mexico Biologics and Reagents Laboratories of Mexico
Russian Federation Chumakov Federal Scientific Center for Research & Development of Immune-and-Biological Products of Russian Academy of Sciences
Serbia Torlak Institute of Virology, Vaccines and Serum
Viet Nam Center for Research and Production of Vaccines and Biologicals

**Numbered notes shown in Fig. 2.1 and Fig. 2.2**

2. WHO master seed stock.
4. Type 1 seed stock prepared at JPRI by four passages of SOM, including three terminal dilution passages (passage level SO+5). Type 2 seed stock prepared at JPRI by one passage of SOM (SO+2).
5. Seed stock prepared at JPRI by one passage of SOB (SO+2).
6. Novartis performed an additional passage to prepare sub-master seed stock from which a working seed was produced.
7. Six plaques were selected, pooled and grown to produce seed stock in the Russian Federation.
10. Produced by JPRI in 1969 from SO stock by one passage (SO+1).
11. Prepared from SOJ by passages in AGMK cells (SOJ+9), including two plaque purifications and three terminal passages (SO+10).
12. Prepared from SOJ by passages in AGMK cells (SOJ+6), including two plaque purifications (SO+7).

Fig. 3 shows a schematic representation of the nOPV2 genome showing modifications and their locations. The sequence of 5’ UTR domain V (S15 domV) prevents an increase in domV thermostability by single point mutations; to prevent replacement of domV attenuation elements by recombination, the cre element, essential for poliovirus replication, was relocated from its original position in the 2C coding region to the 5’ UTR (5’ cre5). The original cre was
inactivated by mutations (cremut); 3Dpol mutations HiFi (D53N) and Rec1 (K38R) reduce overall virus adaptation capacity by reducing mutation and recombination rates, respectively.

Fig. 3
nOPV2 vaccine design

Source: Yeh et al. (2020) (4)

References
Appendix 2

In vivo tests for neurovirulence and considerations in relation to assay choice

Live attenuated poliomyelitis vaccines were developed by Sabin in large part through the use of nonhuman primates, particularly old world monkeys, to measure the level of residual neurovirulence. In the 1980s, tests of vaccine bulks and seeds were standardized as a single dose of test material given by intraspinal inoculation and tested concurrently with an homologous reference preparation. Vaccines derived from the Sabin strains that pass the monkey neurovirulence test (MNVT) have been shown to have an acceptable safety profile. However, in its current form, the MNVT is regarded as a test of consistency and it is not known whether vaccines that fail the test are virulent in human recipients. Tests designed to replace the MNVT should be able to detect the same changes from batch to batch with similar sensitivity. As an alternative to the MNVT for all three poliovirus serotypes, transgenic mice expressing the human poliovirus receptor (TgPVR21 mice) are used in the transgenic mouse neurovirulence test (TgmNVT).

Summaries of the MNVT and TgmNVT for Sabin OPV are given below, along with the implementation process for the TgmNVT. It is assumed that the in vivo neurovirulence test procedures and acceptance criteria applied to Sabin OPV are suitable for the evaluation of nOPV.

1. Summary of the MNVT

1.1 Key features

Detailed standard operating procedures (SOP) for the MNVT are available from WHO. Between 5.5 and 6.5 log_{10} CCID_{50} of monovalent virus is delivered in a single dose by intraspinal inoculation into the lumbar cord. A back titration of the inoculum should be carried out after the inoculation step is completed. Residual paralysis, if any, is noted over the following 17–22 days. The animals are sacrificed at the end of the test or earlier on humane grounds and prepared for histological examination of the central nervous system. Regions are scored for damage on a scale from 1 to 4, and a mean lesion score is calculated for each monkey and then for all the monkeys in the test. The clinical signs do not form part of the assessment or of the pass/fail criteria. The homologous WHO/SO+2 reference

22 See: https://www.who.int/publications/m/item/neurovirulence-test-of-types-1-2-or-3-opv-in-monkeys.
preparation is tested in parallel. For a new laboratory, the implementation process should be agreed with the NRA.

1.2 Number of animals

The number of monkeys has been chosen on statistical grounds, taking into consideration the variability of the test. Valid animals must show some sign of histological damage as evidence of correct placement of active virus. The number of valid monkeys required per virus preparation is 11 for types 1 and 2 and 18 for type 3. Because a reference preparation must be tested at the same time, the total number of monkeys is at least 22 for types 1 and 2 and 36 for type 3.

1.3 Sections examined

Sections are examined from defined regions of the spinal cord and brain and scored histologically for virus activity on a scale of 1 (cellular infiltration only) to 4 (massive neuronal damage). At least 29 sections are examined per monkey, as specified in the WHO SOP for the MNVT. The readings are used to generate the mean lesion score for the animal, and the mean lesions scores for all animals are then used to generate the mean lesion score for the test as a whole.

1.4 Pass/fail criteria

The pass/fail criteria are based on the variation in the test from run to run, established from the scores obtained with the reference preparation and specific to each laboratory and operator. The within-test variance is used to calculate the statistical constants $C_1$, $C_2$ and $C_3$. If the mean lesion score of the test vaccine is greater than that of the concurrently tested reference preparation by more than $C_1$, the vaccine is not acceptable. If the test vaccine gives a higher score than the reference but the difference in scores lies between $C_1$ and $C_2$, the vaccine may be re-tested and the results pooled; if the difference for the pooled test results is greater than $C_3$, the vaccine fails.

The values for $C_1$, $C_2$ and $C_3$ are initially established on the basis of the data accumulated after four qualifying tests. These values should then be updated after every test until nine tests have been performed. After that, the $C$ values are based on the last 10 tests performed. The $C$ values must be established for each testing laboratory.
2. Summary of the TgmNVT

2.1 Key features

Detailed SOP for the TgmNVT are available from WHO. The test for neurovirulence of polio vaccines in transgenic mice involves the intraspinal inoculation of a defined strain of transgenic mice carrying the human receptor for poliovirus with small volumes of the test vaccine. Two virus concentrations are used and the read-out of the test is based on the clinical dose response. A reference preparation is tested at the same time and a clearly defined process has been established for the implementation of the test in a new laboratory.

2.2 Strain of transgenic mouse

Different transgenic mouse lines differ in their sensitivity to poliovirus infection depending on the particular transgenic construct and the genetic background, and only strains from a source approved by WHO should be used. Currently, the only approved transgenic mouse strain is TgPVR21, developed in Japan and sourced from the developers or from an approved subcontractor.

2.3 Titration of virus

Two doses of virus are inoculated in a volume of 5 µL: for type 1, the two doses to be used are 1.75 and 2.75 CCID50; for type 2, 5.0 and 6.0 CCID50; and for type 3, 3.5 and 4.5 CCID50. The inocula must be prepared and titrated accurately to ensure that these doses are given, with a precision of dose determinations better than ± 0.3 log10. A back titration of the inoculum should be performed after the inoculation step is completed.

2.4 Inoculation and observation of animals

Animals procured at age 5–6 weeks are randomized to cages and allowed to recover for at least 7 days. They are then appropriately anaesthetized and inoculated with 5 µL of diluted test virus between the last thoracic and first lumbar vertebrae. Animals are observed for clinical signs once a day for the next 14 days and ultimately scored either as normal (slight weakness or no signs) throughout or paralysed (paresis on two consecutive days or paralysis on a single day). For the test to be valid, the lower and higher doses of the reference preparation should result in more than 5% and less than 95% of the animals becoming paralysed, respectively. A test requires 128 mice for one vaccine plus the reference preparation tested concurrently, or 192 for two vaccines and the reference preparation. The reference preparation is the same as that used in the

23 Available at: https://www.who.int/publications/m/item/neurovirulence-test-sop-of-types-1-2-or-3-opv-in-transgenic-mice-susceptible-to-poliovirus-v8.
MNVT; the use of other reference preparations may be acceptable but should be validated.

The vaccine passes if it is not significantly more virulent than the reference preparation defined in terms of the log odds ratio and statistical constants L1 and L2 which are based on the reproducibility of the test and which define the pass/fail criteria and the grey zone in which a re-test is required. The acceptance and rejection limits, L1 and L2, were selected so that a test vaccine which is equivalent to the reference preparation will have a 0.95 probability of passing and a 0.01 probability of failing, respectively. The constants are regularly updated. Statistical evaluation of test validity includes linearity and dose and gender effects.

3. Implementation process of the TgmNVT

If a manufacturer wishes to use the transgenic mouse test for Sabin OPV, relevant validation data should be available for their specific product to demonstrate the applicability of the test. This may include reference to the extensive collaborative studies through which the test was originally developed. A clear stepwise process for implementing the TgmNVT has been established which involves training in the inoculation technique through the injection of Indian ink, tests with vaccines, and testing of a blinded evaluation panel containing vaccines that pass, fail or marginally fail the test. Competence in clinical scoring is acquired through a standardized training procedure which involves parallel scoring with an experienced scorer, and criteria for declaring a trainee to be competent.

Testing should be performed according to the procedures specified in the WHO SOP for the TgmNVT using appropriate WHO reference materials, unless modified procedures have been validated and shown to be suitable. The test chosen should be used to test virus seeds and bulks, as described in Part A above.

4. Considerations in the choice of assay for the evaluation of Sabin OPV

The following issues highlight that care should be taken in the selection of the in vivo test(s) to be performed for neurovirulence, and that the selection should be justified. The report of the WHO working group meeting to discuss the revision of the WHO Recommendations for OPV: TRS No. 904 and 910 provides more detailed discussion of this (1).

4.1 Types 1 and 2 Sabin vaccine viruses

The sensitivity of the transgenic mouse and monkey NVTs performed according to WHO procedures with respect to the presence of mutations in the 5’ UTR
in types 1 and 2 appears to be comparable, but significantly lower than that for type 3 (2, 3). It is unknown whether these two models are equally sensitive to other potentially neurovirulent mutations. Most manufacturers use essentially identical seeds of types 1 and 2, in contrast to the situation with type 3.

4.2 Type 3 Sabin vaccine virus

4.2.1 Molecular biology

Studies of the molecular biology of Sabin polio vaccine virus strains have suggested that few mutations are involved in attenuation and that, for the type 3 strain, there may be only two – namely, one base change in the 5’ UTR of the genome at base 472 and one coding change at base 2034 that introduces an amino acid change in the virus protein VP3. A third mutation at position 2493 has also been described (4). Growth of Sabin 3 virus in cell culture or in vaccine recipients results in rapid accumulation of U instead of C at nucleotide 2493 (changing Thr to Ile at amino acid 6 of capsid protein VP1), and all Sabin 3 OPV batches contain variable amounts of these mutants. Although this mutation does not affect neurovirulence as determined in the MNVT (5), there is evidence that it influences the results obtained in the TgmNVT, as described in the WHO SOP. Variations in the virulence of vaccine batches measured in monkeys correlate well with variations in the base in the 5’ UTR as measured by MAPREC (5). Amino acid change in VP3, or changes at other positions that suppress its effect, are not thought to be generated in the course of well-controlled production runs – though this is possible in principle.

4.2.2 Current type 3 seed viruses

Seed viruses currently used for global vaccine production contain variable proportions of the bases found at position 2493 (C or U):

- The original WHO reference preparation (passage level SO+2) for neurovirulence testing contained an approximately equal mixture of both forms (2493 C or U).
- Batches prepared from RSO, the seeds most commonly used in production in Europe, typically contain around 5% or less of 2493-U (mutant).
- Seed viruses used in production by some manufacturers (plaque-purified from SO) contain 100% of the mutant form (2493-U) (6).

All OPVs currently in use are believed to have an acceptable safety profile.
5. Experience in using the MNVT and TgmNVT with type 3 Sabin seeds and vaccines

There is evidence that the TgmNVT, as described in the relevant WHO SOP, is sensitive to the presence of 2493-U, whereas the MNVT is not. Thus, batches produced from RSO seed will pass both types of NVT, whereas batches produced from the alternative seeds that contain 100% 2493-U will pass the MNVT but may fail the TgmNVT – despite still having an acceptable safety profile in clinical use.

The current WHO SOP for the TgmNVT specify the doses and the WHO reference material to be used, and state the proportion of mice that must be affected at the two doses of virus given for the test to be valid. The WHO reference material for the TgmNVT is the same as that used in the MNVT and has approximately 50% 2493-C – and was validated primarily against vaccines made from SO or RSO seeds. However, if used to test vaccines derived from 2493-U-containing seed, it may fail them even if they contain little 472-C and would pass the MNVT. The TgmNVT could be adapted for testing 2493-U-containing bulks – for example, by changing the reference material, the doses and/or the validity criteria. Manufacturers may wish to do this to make it applicable to their product. Any modified test should be validated, and should be approved by the NRA.

References


Appendix 3

Example flowsheet of cell culture tests performed during production of poliomyelitis vaccines (oral, live, attenuated) using cell banks

<table>
<thead>
<tr>
<th>Day</th>
<th>0</th>
<th>7</th>
<th>14</th>
<th>21</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled fluid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoenzyme analysis immunological tests, or cytogenic marker tests</td>
<td>10 ml CL</td>
<td>10 ml SC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell banks shall be characterized according to the appropriate Recommendations (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human diploid cells shall be characterized according to the appropriate Recommendations (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Production</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95%</td>
<td>0</td>
<td>4</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harvest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutralized single harvest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 ml HC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 ml other sensitive cell system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Control cells – 5% of the total or 500 mL of cell suspension, or 100 million cells. HAEM = test for haemadsorbing viruses. CL = cell line used for production, but not the same batch of cells used for production of the virus.
SC = when a human diploid cell line is used for production, a simian kidney cell line should be used as the second indicator cell line. When a simian kidney cell line is used for production, a human diploid cell line should be used as the second indicator cell line (1).

HC = human cells.

Note: this example flowsheet includes all tests, whether obligatory or not. Since the requirements applicable in a particular place are those authorized by the NRA, this flowsheet should not be considered as an integral part of such requirements and is provided here solely for guidance. Manufacturers should prepare their own flowsheet in order to clarify the procedures to be used.

Reference

Appendix 4

Cell culture techniques for determining the virus content of poliomyelitis vaccines (oral, live, attenuated)

This appendix describes a method for determining the virus content of live attenuated OPV in cell cultures. This example method is provided for guidance only.

The preparation to be assayed and the reference material are diluted in an appropriate medium. It is convenient to make tenfold dilution steps of the virus suspensions initially but for dilutions that are to be inoculated into Hep-2 (Cincinnati) cell cultures the dilutions should be prepared in 1.0 log10 or smaller steps. A preliminary assay may be required to ensure that, in the test, the dilution range selected encompasses at least three dilutions that will infect between 0% and 100% of the cultures inoculated.

Titrate the vaccine for infectious virus using no fewer than three separate containers of vaccine following the method described below. Titrate one container of an appropriate virus reference preparation in triplicate to validate each assay run. The virus titre of the reference preparation is monitored using a control chart, and a titre is established on an historical basis by each laboratory. If the vaccine contains more than one poliovirus serotype, titration of the individual serotypes is undertaken separately using mixtures of appropriate type-specific antiserum (or preferably a monoclonal antibody) to neutralize each of the other serotypes present.

For titration of the individual serotypes, inoculate a suitable number of wells (ideally 8–10) in a flat-bottomed microtitre plate with equal volumes of the selected dilutions of virus and the appropriate antiserum mixture. Total virus content is determined, without any prior incubation, by directly diluting the vaccine in the assay medium. The assay is then incubated for 1–3 hours at 34–36 °C, followed by the addition of an appropriate volume of a suitable cell. The plates are further incubated at 34–36 °C and examined between day 5 and day 9 for the presence of viral cytopathic effect.

The cytopathic effect can be observed by direct reading or after appropriate staining (vital or fixed staining). The individual virus concentration of each poliovirus serotype and reference preparation is then calculated using an appropriate method.

The assay is considered valid if:

- the estimated virus concentration for the reference preparation is within ± 0.5 log10 CCID50 of the established value for this preparation; and
- the confidence interval ($P = 0.95$) of the estimated virus concentration of the three replicates of the reference preparation is not greater than $\pm 0.3 \log_{10} \text{CCID}_{50}$.

The assay is repeated and results are averaged if:

- the confidence interval ($P = 0.95$) of the combined virus concentration of the vaccine is greater than $\pm 0.3 \log_{10} \text{CCID}_{50}$.

The assay should be validated for nOPV.
Appendix 5

Model summary protocol for the manufacturing and control of poliomyelitis vaccines (oral, live, attenuated)

The following protocol is intended for guidance and indicates the minimum information that should be provided by the manufacturer to the NRA or NCL.

Information and tests may be added or omitted as necessary with the approval of the NRA or NCL. In cases where the testing method is different from the one listed in this model protocol, it should be approved by the NRA. For example, if molecular methods (such as NAT and HTS) are used for the testing of adventitious agents or mycoplasmas, their key parameters and information should be identified and provided, covering, as a minimum, the testing method, date of testing, specification and result.

It is possible that a protocol for a specific product may differ in detail from the model provided here. The essential point is that all relevant details demonstrating compliance with the licence and with the relevant WHO recommendations for a particular product should be provided in the protocol submitted.

The section concerning the final product must be accompanied by a sample of the label and a copy of the leaflet (package insert) that accompanies the vaccine container. If the protocol is being submitted in support of a request to permit importation, it should also be accompanied by a lot release certificate (see Appendix 6 below) from the NRA or NCL of the country in which the vaccine was produced and/or released stating that the product meets the national requirements as well as Part A of these WHO Recommendations.

Summary information on finished product (final vaccine lot)

International name: ____________________________________________
Trade name: ___________________________________________________
Product licence (marketing authorization) number: _________________
Country: _______________________________________________________
Name and address of manufacturer: _________________________________
Name and address of licence holder, if different: _____________________
Virus strain: ___________________________________________________
Origin and short history: _________________________________________
Finished product (final lot): ________________________________
Batch number: __________________________________________
Final bulk: _____________________________________________
Type of container: _______________________________________
Number of doses per container: ____________________________
Number of filled containers in this final lot: ________________
Bulk numbers of monovalent bulk: ________________________
- Type 1: _____________________________________________
- Type 2: _____________________________________________
- Type 3: _____________________________________________
suspensions blended in monovalent/bivalent/trivalent vaccine:
Site of manufacture of each monovalent bulk: _______________
Date of manufacture of each monovalent bulk: _______________
Date of manufacture of final bulk (blending): ________________
Date of manufacture (filling) of finished product: _____________
Date on which last determination of virus titre was started, or date of start of period of validity: ________________
Shelf-life approved (months): _____________________________
Expiry date: __________________________________________
Storage conditions: _____________________________________
Volume of human dose (in drops and/or mL): ________________
Virus titre per single human dose: _________________________
- Type 1: _____________________________________________
- Type 2: _____________________________________________
- Type 3: _____________________________________________
Nature and concentration of stabilizer: _____________________
Nature of any antibiotics present in vaccine and amount per human dose: ________________________________
Release date: _________________________________________

Summary of source materials

The information requested below is to be presented on each submission. Full details on master and working seed lots should be provided upon first submission only and whenever a change has been introduced.

The following sections are intended for recording the results of the tests performed during the production of the vaccine, so that the complete document will provide evidence of consistency of production. If any test has to be repeated, this must be indicated. Any abnormal result must be recorded on a separate sheet.

If any cell lot or virus harvest intended for production is rejected during the control testing, this should also be recorded either in the following sections or on a separate sheet.
Control of source materials (section A.3)

Cell banks (every submission)

Information on cell banking system: ____________________________
Name and identification of substrate: ____________________________
Origin and short history: ____________________________
Authority that approved the cell bank: ____________________________
Master cell bank (MCB) and working cell bank (WCB) lot numbers and date of preparation: ____________________________
Date the MCB and WCB were established: ____________________________
Date of approval by NRA: ____________________________
Total number of ampoules stored: ____________________________
Passage level (or number of population doublings) of cell bank: ____________________________
Maximum passage approved: ____________________________
Storage conditions: ____________________________
Method of preparation of cell bank in terms of number of freezes, and efforts made to ensure that an homogeneous population is dispersed into the ampoules: ____________________________

Tests on MCB and WCB – first submission only

Percentage of total cell bank ampoules tested: ____________________________

Identification test
Method: ____________________________
Specification: ____________________________
Date of test: ____________________________
Result: ____________________________
Growth characteristics: ____________________________
Morphological characteristics: ____________________________
Immunological marker: ____________________________
Cytogenetic data: ____________________________
Biochemical data: ____________________________
Results of other identity tests: ____________________________

Tests for adventitious agents
Method used: ____________________________
Number of vials tested: ____________________________
Volume of inoculum per vial: ____________________________
Tests for bacteria, fungi and mycoplasmas

Tests for bacteria and fungi

Method used: __________________________________________________________

Number of vials tested: ________________________________________________

Volume of inoculum per vial: ____________________________________________

Volume of medium per vial: _____________________________________________

Observation period (specification): ________________________________________

<table>
<thead>
<tr>
<th>Incubation</th>
<th>Media used</th>
<th>Inoculum</th>
<th>Date of start of test</th>
<th>Date of end of test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–25 °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–36 °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative control:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for mycoplasmas

Method used: __________________________________________________________

Volume tested: _________________________________________________________

Media used: ____________________________________________________________

Temperature of incubation: _____________________________________________

Observation period (specification): ________________________________________

Positive controls (list of species used and results): ________________________

<table>
<thead>
<tr>
<th>Subcultures at day 3:</th>
<th>Date of start of test</th>
<th>Date of end of test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcultures at day 7:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcultures at day 14:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcultures at day 21:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Indicator cell culture method (if applicable)

Cell substrate used: _____________________________________________________

Inoculum: ______________________________________________________________

Date of test: ____________________________________________________________________________

Passage number: __________________________________________________________________________
Negative control: ________________________________
Positive controls: ________________________________
Date of staining: ________________________________
Results: ________________________________
Results of tests for tumorigenicity (if applicable): ________________________________

**Virus seed (section A.3.2) – every submission**

Vaccine virus strain(s) and serotype(s): ________________________________
Substrates used for preparing seed lots: ________________________________
Origin and short history: ________________________________
Authority that approved virus strains: ________________________________
Date of approval: ________________________________

**Information and seed lot preparation (section A.3.2.1) – every submission**

Virus master seed (VMS), virus sub-master seed, and virus working seed (VWS)

Source of VMS: ________________________________
VMS and VWS lot number: ________________________________
Name and address of manufacturer: ________________________________
VWS passage level from VMS: ________________________________
Dates of inoculation: ________________________________
Dates of harvest: ________________________________
Number of containers: ________________________________
Conditions of storage: ________________________________
Dates of preparation: ________________________________
Maximum passage levels authorized: ________________________________

**Tests on VMS, virus sub-master seed and VWS – first submission only**

Test for adventitious agents

Date(s) of satisfactory test(s) for freedom from adventitious agent: ________________________________
Volume of virus seed samples for neutralization and testing: ________________________________
Batch number of antisera used for neutralization of virus seed: ________________________________
Method used: ________________________________
Date of start of test: ________________________________
Date of end of test: ________________________________
Result: ________________________________
Identity test
Method used: ______________________________________________________
Date of start of test: _______________________________________________
Date of end of test: ________________________________________________
Result: __________________________________________________________

Absence of SV40
Method used: ______________________________________________________
Date of start of test: _______________________________________________
Date of end of test: ________________________________________________
Results: __________________________________________________________

In vitro tests for molecular characteristics
MAPREC (for Sabin OPV)
Date of test: ______________________________________________________

Type 1
Ratio of % of the sum of both mutations 480-A, 525-C of bulk sample to the International Standard or level of mutations: ______________________________
Result of test of consistency of production: ____________________________
Result of test of comparison with the International Standard: __________

Type 2
Ratio of % 481-G of bulk sample to the International Standard or level of mutations: ______________________________
Result of test of consistency of production: ____________________________
Result of test of comparison with the International Standard: __________

Type 3
Ratio of % 472-C of bulk sample to the International Standard or level of mutations: ______________________________
Result of test of consistency of production: ____________________________
Result of test of comparison with the International Standard: __________
HTS (for virus seed, if applicable)  
<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specification:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of test:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Result:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**In vivo tests for neurovirulence**

**Neurovirulence test in monkeys**

Result of blood serum test in monkeys prior to inoculation:

Number and species of monkeys inoculated:

Quantity (CCID₅₀) inoculated in each test monkey:

Number of “valid” monkeys inoculated with test sample:

Number of positive monkeys observed inoculated with test sample or with reference:

Reference preparation:

Number of “valid” monkeys inoculated with reference:

Number of positive monkeys observed:

Mean Lesion Score of test sample:

Mean Lesion Score of reference:

(see also attached forms giving details of histological observations and assessment)

C1 constant value:

**Neurovirulence test in transgenic mice**

Strain of mice inoculated:

*For each dose of the virus seed sample:*

Number of mice inoculated:

Number of mice excluded from evaluation:

Number of mice paralysed:

*Results of validity tests for each dose of the reference virus:*

Number of mice inoculated:

Number of mice excluded from evaluation:

Number of mice paralysed:

Virus assay results for each dose inoculated (residual inoculum):

Paralysis rates for test vaccine at each dose:

Paralysis rates for reference virus at each dose:
Results: 
Log odds ratio: 
L1 and L2 values: 
Pass/fail decision: 

**Freedom from bacteria, fungi and mycoplasmas**

**Tests for bacteria and fungi**

Method used: 
Number of vials tested: 
Volume of inoculum per vial: 
Volume of medium per vial: 
Observation period (specification): 

<table>
<thead>
<tr>
<th>Incubation</th>
<th>Media used</th>
<th>Inoculum</th>
<th>Date of start of test</th>
<th>Date of end of test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–25 °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–36 °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative control:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test for mycoplasmas**

Method used: 
Volume tested: 
Media used: 
Temperature of incubation: 
Observation period (specification): 
Positive controls (list of species used and results): 

<table>
<thead>
<tr>
<th>Subcultures at day 3:</th>
<th>Date of start of test</th>
<th>Date of end of test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcultures at day 7:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcultures at day 14:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcultures at day 21:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Indicator cell culture method (if applicable)**

Cell substrate used: 
Inoculum: 
Date of test: 
Passage number: 
Negative control: 
Positive controls: 
Date of staining: 
Results: 

**Virus titration**
Date of test: 
Reference batch number: 
Date of test: 
Result: 

**Genotype characterization**
Method used: 
Date of test: 
Result: 

**Test for mycobacteria**
Method used: 
Date of start of test: 
Date of end of test: 
Result: 

**Control of vaccine production (section A.4)**

**Control of production cell cultures**
Lot number of MCB: 
Lot number of WCB: 
Date of thawing of ampoule of WCB: 
Passage number of production cells: 
Date of preparation of control cell cultures: 
Results of microscopic observation: 

**Tests on control cell cultures**
Ratio of control to production cell cultures: 
Incubation conditions: 
Period of observation of cultures: 
Dates observation started/ended: 
Ratio or proportion of cultures discarded for any reason: ______________________
Results of observation: ________________________________________________
Date of supernatant fluid collection: ____________________________________

**Tests for haemadsorbing viruses**
Quantity of cell tested: ________________________________________________
Method used: _________________________________________________________
Date of start of test: _________________________________________________
Date of end of test: _________________________________________________
Results: _____________________________________________________________

**Tests for adventitious agents in cell supernatant fluids**
Method used: _________________________________________________________
Date of start of test: _________________________________________________
Date of end of test: _________________________________________________
Result: ____________________________________________________________

**Identity test**
Method used: _________________________________________________________
Date of start of test: _________________________________________________
Date of end of test: _________________________________________________
Result: ____________________________________________________________

**Control of single harvests (section A.4.3)**
Lot number(s) _________________________________________________________
Date of inoculation: _________________________________________________
Temperature of incubation: _____________________________________________
Date of harvest: _____________________________________________________
Volume harvested: ____________________________________________________
Storage time and approved storage period: _______________________________
Date of sampling: ____________________________________________________

**Identity test**
Method used: _________________________________________________________
Date of start of test: _________________________________________________
Date of end of test: _________________________________________________
Result: _____________________________________________________________
**Virus titration**

Method used: .................................................................
Lot number of reference material: .....................................
Date of start of test: ..................................................
Date of end of test: ..................................................
Result: ........................................................................
Result for reference material: ........................................

**Tests of neutralized single harvests for adventitious agents**

Method used: .................................................................
Date of start of test: ..................................................
Date of end of test: ..................................................
Result: ........................................................................

**Freedom from bacteria, fungi and mycoplasmas**

Tests for bacteria and fungi

Method used: .................................................................
Number of vials tested: ..................................................
Volume of inoculum per vial: ...........................................
Volume of medium per vial: ...........................................
Observation period (specification): ..................................

<table>
<thead>
<tr>
<th>Incubation</th>
<th>Media used</th>
<th>Inoculum</th>
<th>Date of start of test</th>
<th>Date of end of test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–25 °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–36 °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative control:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for mycoplasmas

Method used: .................................................................
Volume tested: ...........................................................
Media used: ..............................................................
Temperature of incubation: ...........................................
Observation period (specification): ............................
Positive controls (list of species used and results):  
........................................................................
### Annex 2

<table>
<thead>
<tr>
<th>Subcultures at day 3:</th>
<th>Date of start of test</th>
<th>Date of end of test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcultures at day 7:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcultures at day 14:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcultures at day 21:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Indicator cell culture method (if applicable)**

- **Cell substrate used:**
- **Inoculum:**
- **Date of test:**
- **Passage number:**
- **Negative control:**
- **Positive controls:**
- **Date of staining:**
- **Results:**

### Test for mycobacteria

- **Method used:**
- **Date of start of test:**
- **Date of end of test:**
- **Result:**

### Tests for molecular consistency

**MAPREC (for Sabin OPV, if applicable)**

- **Date of test:**

#### Type 1

- Ratio of % of the sum of both mutations 480-A, 525-C of bulk sample to the International Standard or level of mutations:
- **Result of test of consistency of production:**
- **Result of test of comparison with the International Standard:**

#### Type 2

- Ratio of % 481-G of bulk sample to the International Standard or level of mutations:
- **Result of test of consistency of production:**
- **Result of test of comparison with the International Standard:**
Type 3
Ratio of % 472C of bulk sample to the International Standard or level of mutations: 

Result of test of consistency of production: 

Result of test of comparison with the International Standard: 

<table>
<thead>
<tr>
<th>HTS (if applicable)</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Result</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Control of monovalent bulk (section A.4.4)
Lot number: 
Date of filtration of bulk: 
Porosity of filters used: 
Date of sampling: 

Identity test
Method used: 
Date of start of test: 
Date of end of test: 
Results: 
Lot number of reference reagents: 

Virus titration
Date of test: 
Reference batch number: 
Result: 

Tests for bacteria and fungi
Method used: 
Number of vials tested: 
Volume of inoculum per vial: 
Volume of medium per vial: 
Observation period (specification): 

<table>
<thead>
<tr>
<th>Incubation Media used</th>
<th>Inoculum Date of start of test</th>
<th>Date of end of test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–25 °C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–36 °C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative control:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test for mycobacteria**

Method used:  
Date of start of test:  
Date of end of test:  
Result:  

**Tests for consistency of virus characteristics**

MAPREC (for Sabin OPV)

Date of test:

**Type 1**

Ratio of % of the sum of both mutations 480-A, 525-C of bulk sample to the International Standard or level of mutations:  
Result of test of consistency of production:  
Result of test of comparison with the International Standard:  

**Type 2**

Ratio of % 481-G of bulk sample to the International Standard or level of mutations:  
Result of test of consistency of production:  
Result of test of comparison with the International Standard:  

**Type 3**

Ratio of % 472C of bulk sample to the International Standard or level of mutations:  
Result of test of consistency of production:  
Result of test of comparison with the International Standard:  
**Neurovirulence tests for Sabin OPV**

**Neurovirulence test in monkeys**

Result of blood serum test in monkeys prior to inoculation: ________________

Date of inoculation of monovalent bulk: ________________

Number and species of monkeys inoculated: ________________

Quantity (CCID$_{50}$) inoculated in each test monkey: ________________

Number of “valid” monkeys inoculated with test sample: ________________

Number of positive monkeys observed inoculated with test sample or with reference: ________________

Reference preparation: ________________

Number of “valid” monkeys inoculated with reference: ________________

Number of positive monkeys observed: ________________

Mean Lesion Score of test sample: ________________

Mean Lesion Score of reference: ________________

(see also attached forms giving details of histological observations and assessment)

C1 constant value: ________________

**Neurovirulence test in transgenic mice**

Strain of mice inoculated: ________________

For each dose of the bulk sample:

Number of mice inoculated: ________________

Number of mice excluded from evaluation: ________________

Number of mice paralysed: ________________

Results of validity tests for each dose of the reference virus: ________________

Number of mice inoculated: ________________

Number of mice excluded from evaluation: ________________

Number of mice paralysed: ________________
Virus assay results for each dose inoculated (residual inoculums): _________________
Paralysis rates for test vaccine at each dose: _________________
Paralysis rates for reference virus at each dose: _________________
Results: _________________

Log odds ratio: _________________
L1 and L2 values: _________________
Pass/fail decision: _________________

**Final bulk (section A.4.5)**

<table>
<thead>
<tr>
<th>Preparation of bulk (types as appropriate):</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monovalent bulks in blend:</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>Volume in blend:</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>Nature and volume of stabilizer:</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>Nature and volume of diluent:</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>Total volume of blend:</td>
<td>_______</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storage time and approved storage period:</td>
<td>_______</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Tests for bacteria and fungi**

<table>
<thead>
<tr>
<th>Method used:</th>
<th>_______</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of vials tested:</td>
<td>_______</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of inoculum per vial:</td>
<td>_______</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of medium per vial:</td>
<td>_______</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation period (specification):</td>
<td>_______</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incubation</th>
<th>Media used</th>
<th>Inoculum</th>
<th>Date of start of test</th>
<th>Date of end of test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–25 °C</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>30–36 °C</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>Negative control:</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
</tbody>
</table>

**Filling and containers (section A.5)**

| Total volume for final filling: | _______ |        |        |
| Date of filling:                | _______ |        |        |
| Number of vials after inspection: | _______ |        |        |
| Number of vials filled:         | _______ |        |        |
Control tests on final lot (section A.6)

Inspection of final containers

Appearance: 

Date of test: 

Results: 

Extractable volume

Extractable volume (mL): 

The number of drops, using the approved dropper, in a minimum of five individual final containers: 

pH

Date of test: 

Result: 

Identity test

Method used: 

Date of start of test: 

Date of end of test: 

Results: 

Lot number of reference reagents: 

Tests for bacteria and fungi

Method used: 

Number of vials tested: 

Volume of inoculum per vial: 

Volume of medium per vial: 

Observation period (specification): 

<table>
<thead>
<tr>
<th>Incubation</th>
<th>Media used</th>
<th>Inoculum</th>
<th>Date of start of test</th>
<th>Date of end of test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–25 °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–36 °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative control:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Virus titration

Date of test: 

Batch number of reference material: ________________________________

Titre of individual virus types: ________________________________

Batch numbers of antiserum used in test: ________________________________

Date of test: ________________________________

<table>
<thead>
<tr>
<th>Results</th>
<th>Vaccine</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type 2:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type 3:</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Thermal stability**

Date of test: ________________________________

Batch numbers of antiserum used in test: ________________________________

<table>
<thead>
<tr>
<th>Results</th>
<th>Vaccine at 37 ºC</th>
<th>Vaccine at storage temperature</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total virus:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Residual antibiotics (if applicable)**

Date of start of test: ________________________________

Date of end of test: ________________________________

Results: ________________________________

**Level of stabilizer (if applicable)**

Date of start of test: ________________________________

Date of end of test: ________________________________

Results: ________________________________

**Additional information for production in monkey kidney cell cultures**

**Production in monkey kidney cell cultures**

Control of vaccine production

**Control of monkeys**

Monkey species used for production: ________________________________

Quarantine batch number: ________________________________

Percentage of monkeys surviving quarantine period: ________________________________

Nature and concentration of antibiotics used in the production cell culture maintenance medium: ________________________________
Tests for antibodies to simian immunodeficiency virus, SV40, foamy viruses and herpes B virus

Methods used: 
Date of start of test: 
Date of end of test: 
Results: 

Production details
Production monkey number: 
Date of trypsinizing: 
Number of cultures prepared: 

Cell cultures for vaccine production
Virus seed lot number: 
Virus titre/cell ratio: 
Number of cultures inoculated: 
Date of inoculation: 
Date of harvest: 
Temperature of incubation: 
Period of incubation: 
Number of cultures harvested: 

Tests on pooled supernatant fluids
Date of sampling from production cell cultures: 
Tests for adventitious agents: 
Volume tested/cell culture type: 
Observation period: 
Date of completion of tests: 
Results: 

Date of sampling from cell cultures inoculated with the pooled fluid 
Tests for adventitious agents: 
Volume tested/cell culture type: 
Date of completion of tests: 
Results: 
Annex 2

Tests in rabbit kidney cell cultures

Volume tested: 

Date of completion of tests: 

Results: 

Control of cell cultures

Ratio of control to production cell cultures or control cell cultures as a proportion of production cell cultures: 

Period of observation of cultures: 

Ratio or proportion of cultures discarded for any reason: 

Results: 

Tests for haemadsorbing viruses

Methods: 

Results: 

Tests for other adventitious agents

Methods: 

Results: 

Control of single harvests

Volume harvested: 

Date of sampling: 

Tests for bacteria, fungi and mycoplasmas: 

Results: 

Tests on neutralized single harvests in monkey kidney cell and human cell cultures

Batch number of antiserum used: 

Volume tested: 

Date of starting primary cell culture tests: 

Period of observation: 

Date of sampling cell culture fluids: 

Period of observation: 

Date of completion of tests: 

Results: 
Control of monovalent bulk
Tests in rabbits
Number and weight of animals: ___________________________________________
Date of inoculation: ___________________________________________________
Results of injection: ___________________________________________________
Quantity injected: ______________________________________________________
Results (survival numbers, etc.): _________________________________________
Date of filtration of bulk: ______________________________________________
Porosity of filters used: _________________________________________________
Date of sampling: _____________________________________________________

Tests for retroviruses
Methods: ______________________________________________________________
Date: __________________________________________________________________
Results: __________________________________________________________________

Certification by the manufacturer

Name of head of production and/or quality control (typed) ______________

Certification by the person from the control laboratory of the manufacturing company taking overall responsibility for the production and quality control of the vaccine:

I certify that lot no. ___________________________ of poliomyelitis vaccine (oral, live, attenuated), whose number appears on the label of the final container, meets all national requirements and/or satisfies Part A24 of the WHO Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated).25

Signature __________________________________________________________________
Name (typed) __________________________________________________________________
Date __________________________________________________________________

24 With the exception of provisions on distribution and transport, which the NRA may not be in a position to assess.
Certification by the NRA/NCL

If the vaccine is to be exported, attach the model NRA/NCL Lot Release Certificate for poliomyelitis vaccines (oral, live, attenuated) (as shown in Appendix 6), a label from a final container and an instruction leaflet for users.
Appendix 6

Model NRA/NCL Lot Release Certificate for poliomyelitis vaccines (oral, live, attenuated)

This certificate is to be provided by the NRA or NCL of the country in which the vaccine has been manufactured, on request by the manufacturer.

Certificate no. ____________________________

The following lot(s) of poliomyelitis vaccine (oral, live, attenuated) produced by ____________________________ 26 in ____________________________, 27 whose numbers appear on the labels of the final containers, meet all national requirements 28 and Part A 29 of the WHO Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated), 30 and comply with WHO good manufacturing practices for pharmaceutical products: main principles; 31 WHO good manufacturing practices for biological products; 32 and the WHO Guidelines for independent lot release of vaccines by regulatory authorities. 33

The release decision is based on ____________________________ 34

Final lot number ____________________________
Number of human doses released in this final lot ____________________________
Expiry date ____________________________

26 Name of manufacturer.
27 Country of origin.
28 If any national requirements have not been met, specify which one(s) and indicate why the release of the lot(s) has nevertheless been authorized by the NRA or NCL.
29 With the exception of provisions on distribution and transport, which the NRA or NCL may not be in a position to assess.
34 Evaluation of the product-specific summary protocol, independent laboratory testing and/or specific procedures laid down in a defined document, and so on as appropriate.
The certificate may also include the following information:

- name and address of manufacturer;
- site(s) of manufacturing;
- trade name and/or common name of product;
- marketing authorization number;
- lot number(s) (including sub-lot numbers and packaging lot numbers if necessary);
- type of container;
- number of doses per container;
- number of containers or lot size;
- date of start of period of validity (for example, manufacturing date) and/or expiry date
- storage conditions;
- signature and function of the person authorized to issue the certificate;
- date of issue of certificate.

The Director of the NRA/NCL (or other appropriate authority):

Signature ___________________________________________________________
Name (typed) _______________________________________________________
Date _______________________________________________________________
Appendix 7

Example flowsheet of cell culture tests performed during production of poliomyelitis vaccines (oral, live, attenuated) using primary monkey kidney cells

HAEM = test for haemadsorbing viruses.
MK = monkey kidney cells from same species (but not the same animal) used for production.
VK = kidney cells from vervet monkey or one sensitive to SV40.
RK = rabbit kidney cells.
HC = human cells sensitive to measles.

**Note:** This example flowsheet includes all tests, whether obligatory or not. Since the requirements applicable in a particular place are those authorized by the NRA, this flowsheet should not be considered as an integral part of such requirements and is provided here solely for guidance. Manufacturing establishments should prepare their own flowsheet in order to clarify the procedures to be used.
Appendix 8

International reference materials for poliomyelitis vaccines (oral, live, attenuated)

This appendix describes the currently available international reference materials for OPV developed for Sabin OPV and available through the MHRA\textsuperscript{35} and WHO\textsuperscript{36} catalogues. International reference materials for nOPV will be needed, particularly WHO international standards for the three serotype versions of nOPV which will likely be required in monovalent and trivalent formulations. Current neurovirulence reference materials used for the MNVT and TgmNVT for Sabin OPV are also suitable for nOPV products. Similarly, international standards for anti-poliovirus antibodies, S19 hyper-attenuated poliovirus strains and anti-polio monoclonal antibody sera are also suitable for nOPV quality control assays. Finally, specific international reference materials for molecular quality control assays based on HTS will be required for Sabin OPV and nOPV products.

WHO international standards and other international reference materials are made available in order to ensure that the manufacture and quality control testing of the different versions of Sabin OPV meet appropriate regulatory requirements.

WHO international standards for the potency testing of tOPV have been available since 1995. More recently, new WHO international standards have been established for bOPV, mOPV1, mOPV2 and mOPV3, with compositions and potencies similar to the vaccines needed for the final phase of the GPEI.

The WHO International Reference Reagent for the potency estimation of OPV (NIBSC code 85/659) was established by the WHO Expert Committee on Biological Standardization (ECBS) in 1995 as a mixture of three commercially produced monovalent bulks – one of each poliovirus (Sabin) types 1, 2 and 3 (1). Following depletion of stocks of this material, the Second WHO International Standard for the potency testing of trivalent OPV (NIBSC code 02/306) was established by the WHO ECBS in 2004 (2), calibrated against 85/659. The composition of the Second WHO International Standard was also kept as close as possible to the previous reference material to allow for the direct comparison of both materials – for example, in stability studies. The Second WHO International Standard was prepared by mixing three commercially

\textsuperscript{35} https://www.nibsc.org/products.aspx  
\textsuperscript{36} https://www.who.int/activities/providing-international-biological-reference-preparations
produced and released monovalent bulks – one of each poliovirus (Sabin) types 1, 2 and 3. The passage level of the virus in the bulks was: Sabin Original (SO)+3 for type 1, SO+3 for type 2 and a re-derived SO (RSO)+3 for type 3. All three bulks used in the production of this standard were produced in primary monkey kidney cells. The standard was prepared by blending the three poliovirus serotype monovalent bulks in MEM with 1% w/v bovine albumin and sodium bicarbonate buffer. The assigned potencies for 02/306 were set at: 7.51, 6.51, 6.87 and 7.66 log_{10} TCID_{50}/mL for types 1, 2, 3 and total virus content, respectively. The same bulk materials used to produce the Second WHO International Standard were also used to prepare candidate preparations for bOPV, mOPV1, mOPV2 and mOPV3 in a similar manner, and these were established as international standards by the WHO ECBS in 2017 (3). The First WHO International Standard for bOPV 1+3 (NIBSC code 16/164) was assigned potencies of 7.19, 6.36 and 7.32 log_{10} TCID_{50}/mL for types 1, 3 and total poliovirus content, respectively. The First WHO international standards for mOPV1 (16/196), mOPV2 (15/296) and mOPV3 (16/202) were assigned potencies of 7.19, 6.36 and 7.32 log_{10} TCID_{50}/mL for types 1, 2 and 3 poliovirus, respectively. Monoclonal antibody sera against types 1, 2 and 3 poliovirus, (NIBSC codes 02/256, 02/258 and 02/260, respectively) are available and routinely used globally by a number of manufacturers and NRAs for potency assays of bOPV and tOPV.

Additionally, low-titre monovalent type 1, 2 and 3 poliovirus WHO reference strains are available for use in reference laboratories to measure the sensitivity of cell cultures to poliovirus infection.

Low-titre monovalent Sabin type 1, 2 and 3 poliovirus reference strains were prepared using the same bulk materials used to produce the current WHO international standards for mOPV, bOPV and tOPV with assigned potencies as follows (4):

- Type 1 (NIBSC code 01/528): 5.1 log_{10} CCID_{50}/0.1 mL in RD cells and 4.9 log_{10} CCID_{50}/0.1 mL in L20B cells;
- Type 2 (NIBSC code 01/530): 5.1 log_{10} CCID_{50}/0.1 mL in RD cells and 4.8 log_{10} CCID_{50}/0.1 mL in L20B cells; and
- Type 3 (NIBSC code 01/532): 5.3 log_{10} CCID_{50}/0.1 mL in RD cells and 4.9 log_{10} CCID_{50}/0.1 mL in L20B cells.

Following depletion of stocks of these reagents, new virus reference stocks were prepared from the same original material. The new monovalent reference reagents were established with assigned potencies as follows:

- Type 1 (NIBSC code 10/164): 5.5 log_{10} CCID_{50}/0.1 mL in RD cells and 5.3 log_{10} CCID_{50}/0.1 mL in L20B cells;
WHO international standards for anti-poliovirus types 1, 2 and 3 antibodies (human) are also available for the standardization of neutralizing antibody tests for poliovirus.

The First WHO international standards for anti-poliovirus sera types 1, 2 and 3 were established by the WHO ECBS in 1963 from serotype-specific polyclonal antisera produced by hyper-immunization of rhesus monkeys with live virus suspensions (5). Each of the standards was specific to one serotype only. They were established through a collaborative study and assigned a unitage of 10 IU/vial for each of the polio serotypes (5). The Second WHO International Standard (NIBSC code 66/202) was established by the WHO ECBS in 1991 to replace the depleted original international standards (6). In contrast to the original international standards, the Second WHO International Standard was a single serum that exhibited activity against each of the three poliovirus serotypes (7). Unitages of 25 IU of anti-poliovirus serum (type 1) human; 50 IU of anti-poliovirus serum (type 2) human; and 5 IU of anti-poliovirus serum (type 3) human were assigned. Following exhaustion of 66/202, the Third WHO International Standard for anti-poliovirus sera (human) types 1, 2 and 3 (NIBSC code 82/585) was established by the WHO ECBS in 2006 with assigned unitages of 11, 32 and 3 IU/vial of neutralizing antibody to poliovirus types 1, 2 and 3, respectively (8).

WHO international standards for MAPREC analysis of poliovirus types 1, 2 and 3 (Sabin) and WHO international reference reagents for the control of MAPREC assays of poliovirus types 1, 2 and 3 (Sabin) are available (9). Some of these reference materials might also be useful for HTS assays (10) or, alternatively, new reference materials might be needed for this purpose.

The WHO international standards and international reference reagents were prepared from commercial vaccines and viruses generated by cell culture infection. The full list of WHO MAPREC reference materials currently available is as follows (11–13):

- NIBSC code 00/410 – MAPREC assay of poliovirus type 1 (Sabin); 100% 480-A, 525-C DNA (WHO International Reference Reagent).
- NIBSC code 00/416 – MAPREC assay of poliovirus type 1 (Sabin); low mutant virus reference (WHO International Reference Reagent).
- NIBSC code 00/418 – MAPREC assay of poliovirus type 1 (Sabin); (First WHO International Standard).
- NIBSC code 00/422 – MAPREC assay of poliovirus type 1 (Sabin); high mutant virus reference (WHO International Reference Reagent).
- NIBSC code 97/758 – MAPREC analysis of poliovirus type 2 (Sabin); synthetic DNA, 0.67% 481-G (First WHO International Standard).
- NIBSC code 98/524 – MAPREC analysis of poliovirus type 2 (Sabin); synthetic DNA, 100% 481-G (First WHO International Standard).
- NIBSC code 98/596 – MAPREC analysis of poliovirus type 2 (Sabin); high virus reference, 1.21% 481-G (WHO International Reference Reagent).
- NIBSC code 94/790 – MAPREC analysis of poliovirus type 3 (Sabin); synthetic DNA, 100% 472-C (First WHO International Standard).
- NIBSC code 95/542 – MAPREC analysis of poliovirus type 3 (Sabin); synthetic DNA, 0.9% 472-C (First WHO International Standard).
- NIBSC code 96/572 – MAPREC analysis of poliovirus type 3 (Sabin); low virus reference, 0.7% 472-C (WHO International Reference Reagent).
- NIBSC code 96/578 – MAPREC analysis of poliovirus type 3 (Sabin); high virus reference, 1.1% 472-C (WHO International Reference Reagent).
- NIBSC code 97/756 – MAPREC analysis of poliovirus type 2 (Sabin); low virus reference, 0.65% 481-G (WHO International Reference Reagent).

Reference materials at the SO+2 passage level (designated WHO/I for type 1 virus, WHO/II for type 2 virus and WHO/III for type 3 virus) are available upon request through WHO. These reference materials are intended for use in the in vivo neurovirulence testing of vaccines. The relevant reference materials should be included in each such test (see section A.4.4.7.2 above). Virus panels for validation and implementation of the TgmNVT, as specified in the WHO SOP (14), are also available.

New non-pathogenic hyper-attenuated poliovirus strains (S19) are available for use in OPV quality control assays (15). S19 strains are polioviruses that replicate in tissue culture but are unlikely to replicate at all in humans exposed even to large amounts. For this reason, they can be used outside GAPIV containment requirements.

The strains are genetically stable and include a portfolio of strains containing the capsid proteins, (and thus possessing the antigenic properties) of the Sabin OPV strains or wild-type strains used most commonly in the production of inactivated polio vaccine. In December 2018, the WHO Containment Advisory Group concluded that S19 strains can be used outside the containment requirements of GAPIV for neutralization assays (16). Organizations wishing to use S19 poliovirus
strains should follow a detailed validation process to ensure that the genetic properties of S19 strains are maintained and can be used to replace current original poliovirus strains. There is a seed lot system for producing banks of highly characterized S19 strains that resembles the vaccine production system. MHRA advises that S19 strains should be tested on a seed lot basis to minimize the risks of reversion and will work with any suitable facility to help generate and validate further banks.

The reference materials listed above are available from MHRA.37

References


37 Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom: https://www.nibsc.org/


Annex 3

WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices

WHO Medical device technical series

1. Introduction 183
2. Purpose and scope 184
3. Terminology 186
4. Definition, classification, essential principles and conformity assessment of medical devices 194
   4.1 Definition of medical device and in vitro diagnostic medical device 194
   4.2 Medical devices classification and classification rules 196
   4.3 Principles of safety and performance 200
   4.4 Specific considerations for regulation of IVDs 205
5. Enabling conditions for effective regulation of medical devices including IVDs 208
   5.1 Legal requirements 208
   5.2 Gap analysis of existing controls 210
   5.3 Implementation plan 213
   5.4 Monitoring implementation 214
   5.5 National regulatory authority 214
   5.6 Funding the regulatory system 215
   5.7 Conflict of interest and impartiality 215
   5.8 Regulatory competencies and resources 216
   5.9 Reliance and recognition 218
6. Establishing a stepwise approach to regulating medical devices 222
   6.1 Stepwise approach 222
   6.2 Basic-level regulatory controls and their enforcement 223
   6.3 Expanded-level regulatory controls and their enforcement 235
   6.4 Stepwise approach – harmonization, reliance and recognition 259
7. Regulatory pathways 261
   7.1 Regulatory pathways for pre-market conformity assessment of medical devices according to risk class 261
   7.2 Regulatory pathways for pre-market conformity assessment of medical devices based on reliance 263
Guidance documents published by the World Health Organization (WHO) are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs).
**Abbreviations**

AI  artificial intelligence
AMDF  Africa Medical Devices Forum
APEC RHSC  Asia Pacific Economic Cooperation Regulatory Harmonization Steering Committee
ASEAN  Association of Southeast Asian Nations
CAB  conformity assessment body
CDx  companion diagnostic in vitro medical device
CRP  collaborative registration procedure
CLSI  Clinical and Laboratory Standards Institute
EMDN  European Medical Device Nomenclature
EU  European Union
EUL  WHO emergency use listing (procedure)
FSCA  field safety corrective action(s)
FSN  field safety notice
GBT  WHO global benchmarking tool
GDP  good distribution practice
GHTF  Global Harmonization Task Force
GMDN  Global Medical Device Nomenclature
GMRF  WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices
GRP  good regulatory practice(s)
HIBCC  Health Industry Business Communications Council
IEC  International Electrotechnical Commission
IEEE  Institute for Electrical and Electronics Engineers
IFU  instructions for use
IMDRF  International Medical Device Regulators Forum
ISO  International Organization for Standardization
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IT</td>
<td>information technology (also ICT = information and communications technology)</td>
</tr>
<tr>
<td>IVD</td>
<td>in vitro diagnostic medical device</td>
</tr>
<tr>
<td>LMIC</td>
<td>low- and middle-income countries</td>
</tr>
<tr>
<td>ML</td>
<td>machine learning</td>
</tr>
<tr>
<td>MLMD</td>
<td>machine learning-enabled medical device</td>
</tr>
<tr>
<td>NRA</td>
<td>national regulatory authority</td>
</tr>
<tr>
<td>PI</td>
<td>product identifier</td>
</tr>
<tr>
<td>PPE</td>
<td>personal protective equipment</td>
</tr>
<tr>
<td>PQ</td>
<td>prequalification of medical products (also WHO PQ)</td>
</tr>
<tr>
<td>QMS</td>
<td>quality management system</td>
</tr>
<tr>
<td>SaMD</td>
<td>software as a medical device</td>
</tr>
<tr>
<td>SDO</td>
<td>standards development organization</td>
</tr>
<tr>
<td>SF</td>
<td>substandard and falsified (medical products)</td>
</tr>
<tr>
<td>SiMD</td>
<td>software in a medical device</td>
</tr>
<tr>
<td>STED</td>
<td>summary technical documentation</td>
</tr>
<tr>
<td>SUMD</td>
<td>single-use medical device</td>
</tr>
<tr>
<td>UDI</td>
<td>unique device identification</td>
</tr>
<tr>
<td>UDI-DI</td>
<td>UDI device identifier</td>
</tr>
<tr>
<td>UDI-PI</td>
<td>UDI production identifier</td>
</tr>
<tr>
<td>UDID</td>
<td>UDI database</td>
</tr>
<tr>
<td>UMDNS</td>
<td>Universal Medical Device Nomenclature System</td>
</tr>
<tr>
<td>USFDA</td>
<td>United States Food and Drug Administration</td>
</tr>
</tbody>
</table>
1. Introduction

The regulation of medical devices including in vitro diagnostics is critical in assuring their quality, safety and performance. In May 2014, the World Health Assembly adopted resolution WHA67.20 on regulatory system strengthening for medical products (1). This underscored the importance of effective regulatory systems as an essential component of health system strengthening and contributor to public health. WHO decided to develop guidance to support countries that had yet to develop and implement, or that were revising, their national regulatory controls for medical devices.

The previous WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices (GMRF) was published in 2017 in English and was then translated into French and Russian. Since then, the GMRF has served as a background document in WHO workshops on medical devices. It was also considered a standard during the integration of medical devices indicators into the development of the WHO global benchmarking tool (GBT), version VI (2, 3). Underpinning the GMRF are the WHO Good regulatory practices in the regulation of medical products (4) and WHO Good reliance practices in the regulation of medical products: high level principles and considerations (5), both published in 2021.

The field of medical devices is rapidly changing. Technologies are advancing with regard to their nature and complexity, and are increasingly being used in less traditional settings such as the home or remote care. In addition, new suppliers are entering the field, often without relevant experience or qualifications, and often with little local regulatory oversight. Jurisdictions are adapting their laws and regulations to ensure the improved and more timely regulation of medical devices in order to protect and promote public health. They have also had to quickly develop the increased regulatory capacities needed to implement those regulations. The COVID-19 pandemic clearly demonstrated the importance and urgency of ensuring equitable and timely access to safe, reliable and appropriate quality medical devices, including in vitro diagnostic medical devices (IVDs). It also highlighted the importance of integrity in domestic and international supply chains for medical devices and related personal protective equipment (PPE). As important as they are, vaccines are not effective if they cannot be safely delivered, while infections cannot be diagnosed and conditions treated without medical devices including IVDs.

The regulation of medical devices involves many stakeholders. The national regulatory authority (NRA) has the authority under laws adopted by legislators to establish and enforce regulatory requirements. Technology developers, manufacturers, and their authorized representatives, importers, distributors and outlets, are all part of supply chains in which the integrity and quality of medical devices must be ensured. Health care professionals,
laboratory staff, and patients or users, should be able to rely on the safety, quality and performance of medical devices, from the simplest to the most advanced, when used as intended. Users and health systems also have a stake in continuing innovation in medical technologies to diagnose and treat conditions for which there are unmet clinical needs.

The GMRF focuses on the responsibilities of the legislator and the NRA in establishing, implementing and enforcing the legal and regulatory framework. It also indirectly outlines the compliance obligations of industry stakeholders. The GMRF recognizes the importance of the health care system in providing feedback on the safety and performance of medical devices.

Many countries have neither the financial resources nor the technical expertise to move from a minimally regulated market directly to one with a comprehensive medical devices law and regulatory controls. The GMRF recommends instead a stepwise approach to regulating the quality, safety and performance of medical devices. This staged development starts from basic-level regulatory controls – such as the publication of the law, import controls, and resourcing the regulatory authority to take enforcement actions – then progresses to expanded-level regulatory controls – such as inspection of registered establishments and oversight of clinical investigations.

The resources available in any country for the regulatory control of medical devices (that is, people, funds, technology and facilities) are – and probably always will be – limited. Mechanisms for benefitting from the regulatory work of other jurisdictions can be established through reliance and recognition – practices well known both to countries with less developed regulatory systems and to mature jurisdictions.

More broadly, it should be understood that the national regulation of medical devices does not take place in isolation, but should be coordinated at a regional and global level.

2. Purpose and scope

This revised GMRF recommends guiding principles and harmonized definitions, and specifies the attributes of effective and efficient regulations to be embodied within binding and enforceable national laws. Its main elements are derived from international regulatory harmonization guidance documents developed by the Global Harmonization Task Force (GHTF) and its successor, the International Medical Device Regulators Forum (IMDRF), along with regional harmonization initiatives. Those guidance documents rely in turn upon a large body of recognized international consensus standards covering specific technical elements in the GMRF. As medical device technology continues to advance, as more experience is gained by regulators and industry, and as medical device regulation spreads
to more countries, this body of guidance will continue to evolve and support broader regulatory convergence.

The GMRF is written for the legislative and executive branches of government as they develop and establish national systems of medical devices regulation. This current version describes the roles and responsibilities of a country’s regulatory authority in implementing and enforcing such regulations. The range of topics has been expanded to include regulatory pathways for the use of reliance and recognition, emergency use authorization, borderline products and donated medical devices, along with policies on medical devices testing and local production. It also addresses new topics such as software as a medical device (SaMD) and combination products, and provides implementation guidance on stakeholder involvement, developing a road map and regulatory capacity-building.

Despite the expanded range of topics covered in this revised GMRF, a number of medical device subjects have not been addressed, including orphan medical devices, off-label use of medical devices, in-house developed medical devices, 3D printing of medical devices and medical device registries. Updates in these areas will be provided in future revisions as more information becomes available.

Section 4 of this document recommends definitions of the terms “medical device” and “in vitro diagnostic medical device”. It describes how devices may be grouped according to their potential for harm to the patient or user, and specifies principles of safety and performance that the device manufacturer must adhere to. It explains how the manufacturer must have a quality management system (QMS) and demonstrate to an NRA that its medical device has been designed and manufactured to be safe and to perform as intended during its life-cycle.

Section 5 presents the principles of good regulatory practices (GRP) and enabling conditions for the effective regulation of medical devices. It then introduces essential tools for regulation, explaining the functions of the regulatory authority and the resources required. Increasingly, and as medical device regulation spreads to low- and middle-income countries (LMIC), the need for collaboration, information exchange and regional harmonization initiatives will grow. Few countries, even those with mature regulatory systems, will have the ability to perform all regulatory functions with their own resources. Reliance and recognition have become more important as ways to protect public health. As countries implement or revise regulatory systems, they should consider which elements must be done at national level and which may be done by relying upon and recognizing the work done by others.

Section 6 presents a stepwise approach to implementing and enforcing regulatory controls for medical devices, as the regulations progress from a basic
to an expanded level. It describes elements from which a country may choose according to its national priorities and challenges.

Section 7 describes the regulatory pathways for different risk classes of medical devices. It provides a clear overview of steps to be taken by the regulatory authority before a medical device may be placed on the market.

Section 8 covers additional topics to be considered when developing and implementing regulations for medical devices. It explains the relevance of these topics and provides guidance for regulatory authorities to ensure that they are appropriately addressed.

Section 9 presents topics that are relevant for the implementation of regulatory controls in an effective manner.

The current document outlines a general approach to the regulation of medical devices including IVDs but, as different countries will have different legal frameworks and policy priorities, it cannot provide country-specific guidance on implementation. While it does not offer detailed guidance on regulatory topics, it does provide references to numerous relevant documents where further information may be found. The GMRF is therefore not intended to be a detailed compendium of all relevant information but rather a “pointer” to guide readers to sources, while aiding understanding of such guidance in the context of a comprehensive regulatory framework. Nor does it directly detail the responsibilities of other stakeholders such as manufacturers, distributors, procurement agencies and health care professionals – all of whom have a role to play in assuring the quality, safety and performance of medical devices.

3. Terminology

The definitions given below apply to the terms as used in this WHO guidance document. These terms may have different meanings in other contexts.

**Accessory to an IVD**: an article intended specifically by its manufacturer to be used together with a particular IVD to enable or assist that device to be used in accordance with its intended use (6).

**Accessory to a medical device**: an article intended specifically by its manufacturer to be used together with a particular medical device to enable or assist that device to be used in accordance with its intended use (6).

**Accreditation**: the term applied to third party attestation related to a conformity assessment body conveying formal demonstration of its competence to carry out specific conformity assessment tasks (7).

**Adverse event and incident**: in this document, the terms “adverse event” and “incident” are both used. The term adverse event denotes an event that impacts the patient while incident denotes events primarily attributed to the medical device. However, it should be noted that, depending on jurisdiction, the
terms adverse event (in the context of post-market surveillance) and incident can be used interchangeably. Further information on the precise meaning of these terms in the context of medical devices including in vitro medical devices can be found in the highly detailed terminological and related guidance provided by IMDRF (8–10) and WHO (11).

**Analytical performance:** the ability of an IVD to detect or measure a particular analyte (12).

**Analytical validation:** measures the ability of software as a medical device (SaMD) to accurately, reliably and precisely generate the intended technical output from the input data (13).

**Assessment:** a systematic, independent, and documented process for obtaining assessment evidence and evaluating it objectively to determine the extent to which assessment criteria are fulfilled (14).

**Audit:** a process for obtaining relevant information about an object of conformity assessment and evaluating it objectively to determine the extent to which specified requirements are fulfilled (7).

**Authorized representative:** any natural or legal person established within a country or jurisdiction who has received a written mandate from the manufacturer to act on its behalf for specified tasks, with regard to the latter’s obligations under that country or jurisdiction’s legislation (15).

**Certification:** the term applied to third party attestation related to products, processes, systems or persons (7).

**Clinical evaluation:** a set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety, clinical performance and/or effectiveness of the medical device when used as intended by the manufacturer (16).

**Clinical evidence:** the clinical data and its evaluation pertaining to a medical device. Clinical evidence is an important component of the technical documentation of a medical device, which along with other design verification and validation documentation, device description, labelling, risk analysis and manufacturing information is needed to allow a manufacturer to demonstrate conformity with the essential principles (see section 4.3 below). It should be cross-referenced to other relevant parts of the technical documentation that impact on its interpretation (17).

**Clinical investigation:** any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety, clinical performance and/or effectiveness of a medical device (18).

**Clinical performance:** the ability of an IVD to yield results that are correlated with a particular clinical condition/physiological state in accordance with target population and intended user. Clinical performance data can be derived from multiple sources such as clinical performance studies, literature or experience gained by routine diagnostic testing (12).
Clinical validation of SaMD: measures the ability of SaMD to yield a clinically meaningful output associated to the target use of SaMD output in the target health care situation or condition identified in the SaMD definition statement (13).

Conflict of interest: as occurring when a public official has private-capacity interests which could improperly influence the performance of their official duties and responsibilities (19).

Conformity assessment: the systematic examination of evidence generated, and procedures undertaken, by the manufacturer, under requirements established by the regulatory authority, to determine that a medical device is safe and performs as intended by the manufacturer and therefore conforms to the essential principles of safety and performance for medical devices (20).

Conformity assessment body (CAB): a body, other than a regulatory authority, engaged in determining whether the relevant requirements in technical regulations or standards are fulfilled (20).

Convergence (regulatory): a voluntary process whereby the regulatory requirements in different countries or regions become more similar or “aligned” over time. Convergence results from gradual adoption of internationally recognized technical guideline documents, standards, scientific principles, common or similar practices and procedures, or the establishment of appropriate domestic regulatory mechanisms that align with shared principles to achieve a common public health goal (4).

Corrective action: action to eliminate the cause of a detected non-conformity or other undesirable situation (21).

Declaration of conformity: a mandatory document that a manufacturer or authorized representative signs to declare that products comply with the regulatory requirements – amended from EU declaration of conformity (22).

Device identifier (DI): a unique numeric or alphanumeric code specific to a model of medical device and that is also used as the “access key” to information stored in a UDI database (UDID) (23).

Distributor: any natural or legal person in the supply chain who, on their own behalf, furthers the availability of a medical device to the end-user (15).

Enforcement: action taken by an authority to protect the public from products of suspect quality, safety and effectiveness, or to assure that products are manufactured in compliance with appropriate laws, regulations, standards and commitments made as part of the approval to market a product (24).

Falsified: denoting medical products that deliberately/fraudulently misrepresent their identity, composition or source (25).

Field safety corrective action (FSCA): an action taken by a manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device. Such actions should be notified via a field safety notice (FSN) (26).
Field safety notice (FSN): a communication sent out by a manufacturer or its representative to the device users in relation to a field safety corrective action (FSCA) (27).

Governance: refers to the different ways that organizations, institutions, businesses and governments manage their affairs. Governance is the act of governing and thus involves the application of laws and regulations, but also of customs, ethical standards and norms (28).

Guidelines/guidance documents: non-statutory advisory publications intended to assist those parties affected by legislation to interpret requirements.

Harm: a physical injury or damage to the health of people, or damage to property or the environment (29).

Harmonization (regulatory): a process whereby the technical guidelines of participating authorities in several countries are made uniform (4).

Hazard: a potential source of harm (29).

Health technologies: the application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of lives (30).

Importer: any natural or legal person in the supply chain who is the first in a supply chain to make a medical device, manufactured in another country or jurisdiction, available in the country or jurisdiction where it is to be marketed (15).

Inspection: examination of an object of conformity assessment and determination of its conformity with detailed requirements or, on the basis of professional judgment, with general requirements (7).

Instructions for use (IFU): information provided by the manufacturer to inform the device user of the medical device’s intended purpose and proper use, and any precautions to be taken (31).

Intended use/purpose: the objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and other information provided by the manufacturer (32).

In vitro diagnostic medical device (IVD): a medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes (6).

Label: written, printed or graphic information either appearing on the medical device itself or on the packaging of each unit or on the packaging of multiple devices (31).

Labelling: the label, IFU and any other information that is related to identification, technical description, intended purpose and proper use of the medical device, but excluding shipping documents (31).

Laboratory: body that performs one or more of the following activities: testing, calibration and/or sampling associated with subsequent testing or
calibration. In the current document “laboratory activities” refer to these three activities (33).

- **Law**: binding and enforceable legislation passed by a legislative body.
- **Lay person**: individual who does not have formal training in a specific field or discipline (31).
- **Life-cycle**: all phases in the life of a medical device, from the initial conception to final decommissioning and disposal.
- **Listing**: the process whereby a party submits information to the regulatory authority in a jurisdiction regarding the identification of a medical device(s) that is or will be supplied to the market in that jurisdiction (34).
- **Machine learning-enabled medical device (MLMD)**: a medical device that uses machine learning (ML), in part or in whole, to achieve its intended medical purpose (35).
- **Manufacturer**: any natural or legal person with responsibility for the design and/or manufacture of a medical device with the intention of making the medical device available for use, under its name; whether or not such a medical device is designed and/or manufactured by that person themselves or on their behalf by another person(s). **Note**: this “natural or legal person” has ultimate legal responsibility for ensuring compliance with all applicable regulatory requirements for the medical device(s) in the countries or jurisdictions where it is intended to be made available or sold unless this responsibility is specifically imposed on another person by the regulatory authority within that jurisdiction (15).
- **Market surveillance**: the activities carried out and measures taken by competent authorities to check and ensure that devices comply with the requirements set out in the relevant legislation and do not endanger health, safety or any other aspect of public interest protection. **Note**: “relevant legislation” has been used here in place of “Union harmonisation legislation” in the EU source document (36).
- **Medical device**: any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific medical purpose(s) of:
  - diagnosis, prevention, monitoring, treatment or alleviation of disease;
  - diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury;
  - investigation, replacement, modification or support of the anatomy or physiological process;
  - supporting or sustaining life;
  - control of conception;
  - cleaning, disinfection or sterilization of medical devices;
- providing information by means of in vitro examination of specimens derived from the human body;

and which does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means (37).

**Medical product**: any product including, but not limited to, finished pharmaceutical products, medical devices including in vitro diagnostic medical devices, and vaccines (38).

**Performance evaluation of an IVD**: assessment and analysis of data to establish or verify the scientific validity and analytical and, where applicable clinical, performance of an IVD (37).

**Personal protective equipment (PPE)**: protective clothing, helmets, gloves, face shields, goggles, facemasks and/or respirators or other equipment designed to protect the wearer from injury or the spread of infection or illness. PPE is commonly used in health care settings such as hospitals, doctor’s offices and clinical laboratories (39).

**Placing on the market**: all controls applied by the NRA to the manufacturer and/or authorized representative at the stage of, and as a condition of, making available an individual medical device with a view to its distribution and/or use within the jurisdiction.

**Post-market controls**: all controls applied by the NRA to the manufacturer and/or authorized representative after a manufacturer’s medical device has been placed on the market or put into service.

**Post-market surveillance**: all activities carried out by manufacturers in cooperation with other economic operators to institute and keep up to date a systematic procedure for proactively collecting and reviewing experience gained from the use of devices they place on the market, make available on the market or put into service for the purpose of identifying any need to immediately apply any necessary corrective or preventive actions (36).

**Pre-market controls**: all controls applied by the NRA to the manufacturer and/or authorized representative before the manufacturer’s medical device may be placed on the market or put into service.

**Primary legislation**: a form of law, created by a legislative branch of government, consisting of statutes that set out broad outlines and principles and may delegate authority to an executive branch of government to issue secondary legislation.

**Primary mode of action**: the single mode of action of a combination product that makes the greatest contribution to the combination product’s overall intended use(s) (40).
Production identifier (PI): a numeric or alphanumeric code that identifies the unit of device production. The different types of PI include serial number, lot/batch number, SaMD version and manufacturing and/or expiration date (23).

Quality management system (QMS): the organizational structure, responsibilities, procedures, processes and resources for implementing quality management. “Implementing quality management” is taken to include both the establishment and maintenance of the system (41).

Recall: any measure aimed at achieving the return of a device that has already been made available to the end-user (36).

Recognition: acceptance of the regulatory decision of another regulator or other trusted institution. Recognition should be based on evidence that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement (5).

Reference regulatory authority: a national or regional authority, or a trusted institution such as WHO prequalification (WHO PQ), whose regulatory decisions and/or regulatory work products are relied upon by a regulatory authority to inform its own regulatory decisions (5).

Refurbishing: reconditioning medical devices for safety and effectiveness with no significant change in their performance, safety specifications or service procedures as defined by the manufacturer and their original intended use (42).

Registration: the process by which a party submits information to the regulatory authority in a jurisdiction regarding the identification and establishment location(s) of the manufacturer and other parties responsible for supplying a medical device(s) to the market in that jurisdiction (34).

Regulation: a written instrument containing rules having the force of law.

Regulatory authority: a government body or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and that may take enforcement action to ensure that medical products marketed within its jurisdiction comply with legal requirements (20).

Reliance: the act whereby a regulatory authority in one jurisdiction takes into account, and gives significant weight to, assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others (5).

Reprocessing: a process carried out on a used device in order to allow its safe re-use, including cleaning, disinfection, sterilization and related procedures,
as well as testing and restoring the technical and functional safety of the used device (43).

**Risk**: the combination of the probability of occurrence of harm and the severity of that harm (29).

**Sameness**: sameness of product means that two products have identical essential characteristics (that is, the product being submitted to the relying authority and the product approved by the reference regulatory authority should be essentially the same) (5).

**Scientific validity**: refers to the extent to which the SaMD’s output (concept, conclusion, measurements) is clinically accepted or well founded (existence of an established scientific framework or body of evidence) that corresponds accurately in the real world to the health care situation and condition identified in the SaMD definition statement (13).

**Secondary legislation**: a form of law, issued by an executive branch of government, specifying substantive regulations and procedures for implementing them. The power to pass delegated legislation is defined and limited by the primary legislation that delegated those powers.

**Self-testing IVD**: an IVD intended for use by a lay user who is responsible for collecting the data or specimen by themselves, relying solely on the instructions provided by the manufacturer. This use can also include performing the test and interpreting the results by themselves and on themselves (44).

**Serious public health threat**: any event type which results in imminent risk of death, serious injury or serious illness that requires prompt medical action. A serious injury is either:

- a life-threatening illness or injury;
- a permanent impairment of a body function or permanent damage to a body structure;
- a condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure (26).

**Single-use medical device (SUMD)** – also referred to in other documents as disposable devices or single-use devices (SUDs): a medical device or IVD medical device that is intended to be used on an individual patient during or for a single procedure and then disposed of. It is not intended to be reprocessed and used again (31).

**Software as a medical device (SaMD)**: software intended to be used for one or more medical purposes and that performs these purposes without being part of a hardware medical device (45).

**Standard**: a document established by consensus and approved by a recognized body that provides, for common and repeated use, rules, guidelines
or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context (46).

**Substandard (also called “out of specification”):** authorized medical products that fail to meet either their quality standards or specifications, or both (25).

**Supply chain:** a collective term for manufacturers, authorized representatives, importers and distributors established internationally or domestically.

**Technical documentation:** the documented evidence, normally an output of the QMS, that demonstrates that the medical device complies with the relevant principles of safety, performance and labelling specified through legislation (20).

**Unique device identification (UDI):** a series of numeric or alphanumeric characters that is created through a globally accepted device identification and coding standard. The UDI allows for the unambiguous identification of a specific medical device on the market and comprises the UDI device identifier (UDI-DI) and UDI production identifier (UDI-PI) (23).

**UDI database (UDID):** the UDID contains identifying information and other elements associated with the specific medical device (23).

**User:** the person, either professional or lay, who uses a medical device. The patient may be the user (31).

**Withdrawal:** any measure aimed at preventing a device in the supply chain from being further made available on the market (36).

### 4. Definition, classification, essential principles and conformity assessment of medical devices

#### 4.1 Definition of medical device and in vitro diagnostic medical device

The GHTF developed definitions of the terms “medical device” and “in vitro diagnostic medical device”. Major jurisdictions have accepted the principles of these definitions. In the interest of international regulatory convergence and harmonization, it is recommended to promote their widespread use.

**Medical device:** any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or

---

38 “In vitro diagnostic medical device” is a synonym of “in vitro diagnostic” and is abbreviated as “IVD“ in the current document.

39 Notes from IMDRF definition (37): Note 1: For clarification purposes, in certain regulatory jurisdictions, devices for cosmetic/aesthetic purposes are also considered medical devices. Note 2: For clarification purposes, in certain regulatory jurisdictions, the commerce of devices incorporating human tissues is not allowed.
related article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific medical purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury;
- investigation, replacement, modification or support of the anatomy or physiological process;
- supporting or sustaining life;
- control of conception;
- cleaning, disinfection or sterilization of medical devices;
- providing information by means of in vitro examination of specimens derived from the human body;

and which does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means (37).

**In vitro diagnostic medical device (IVD):** A medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes (6).

There may also be products on the market that are similar to medical devices in function and risk that do not fit within these definitions. For reasons of public health protection, these may be regulated as if they were medical devices. Examples include: PPE to avoid cross-infection; lead aprons to protect

---

40 Notes from GHTF definition (6): Note 1: IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status. Note 2: In some jurisdictions, certain IVD medical devices may be covered by other regulations.


42 Whether a product is classified as PPE or not depends on the intended purpose of the product. If the product is intended exclusively for the protection of the user (the person wearing it) against one or more health and safety hazards, then it is considered to be PPE. Products intended to protect patients or users are considered to be medical devices. If a product is intended for both purposes, it is both a medical device and PPE (https://www.johner-institute.com/articles/regulatory-affairs/and-more/marketing-personal-protective-equipment-ppe/, accessed 23 January 2023), and may be subject to both regulatory regimes.
against radiation; some medical gases;\textsuperscript{43} and implantable or other invasive products for cosmetic rather than medical purposes, such as dermal fillers (see section 7.4 below).

4.2 Medical devices classification and classification rules\textsuperscript{44}

The universe of medical devices is diverse with wide variations in potential severity of harm to the patient or user. This GMRF recommends that the NRA allocates its resources and imposes controls proportionate to the potential for harm associated with medical devices (32, 44).

Regulations should specify the way in which a manufacturer shall demonstrate conformity with safety, performance and quality requirements. Regulatory oversight should increase in line with the potential of a medical device to cause harm to a patient or user, and with the severity of that harm (that is, the risk it presents). The risk class of a medical device is determined by factors such as the level of invasiveness and duration of use in the body, and whether it incorporates medicines or human/animal tissues/cells. The risk class of an IVD is determined primarily by the impact of an incorrect result, either on the health of the individual or on public health. A classification system for medical devices and IVDs will guide the regulatory controls to be implemented for each device class.

It is widely accepted that medical devices can be separated into groups or classes – typically the four classes A, B, C and D\textsuperscript{45} – by applying a set of risk-based classification rules (32) and specifying separately the different conformity assessment procedures that should apply to each group of devices (Fig. 4.1). A medical device can generally be classified to one risk class. If, however, more than one risk class could apply, the higher class shall be applied.

\textsuperscript{43} Gases intended for administration to a patient are regulated as medicinal products, whereas the associated administration equipment is regulated as a medical device(s). Some gases used for medical purposes may also be classified as medical device gases where they do not have a specific intended therapeutic outcome for the patient. Medical gases that are considered medical devices have a mechanical or physical action (that is, they do not act by immunological, metabolic or pharmacological means). Examples include gases for insufflation of the abdominal wall during surgery and liquid nitrogen for the removal of warts (https://bcqa.co.uk/topics/medical-gases/, accessed 23 January 2023).

\textsuperscript{44} The terms “medical devices classification” and “medical devices risk classification” are interchangeable.

Fig. 4.1  
Impact of device classification on regulatory scrutiny

![Diagram showing impact of device classification on regulatory scrutiny](image)

Note: as the regulatory requirements increase, so does the scrutiny by the NRA.  
Source: reproduced from *Principles of medical devices classification* (32).

The classification rules for medical devices other than IVDs depend on the features of the device, such as whether it:

- is life supporting or sustaining
- is invasive and if so, to what extent and for how long
- incorporates medicinal products
- incorporates human or animal tissues or cells
- is an active medical device
- delivers medicinal products, energy or radiation
- could modify blood or other body fluids
- is used in combination with another medical device.

The classification of medical devices including IVDs also takes into account the technical, scientific and medical expertise of the intended user (lay person or health care professional). The use of medical devices by lay persons places specific requirements on the manufacturer to provide necessary ergonomic features to ensure a high likelihood of correct use and to provide information and instruction on the labelling to ensure safe and effective use.

For IVDs, the risk classification depends both on the risk to the individual and to public health, taking into consideration:
- the intended use and indications for use as specified by the manufacturer;
- the technical/scientific/medical expertise of the intended user (lay person or health care professional);
- the importance of the information to the diagnosis (sole determinant or one of several), taking into consideration the natural history of the disease or disorder including presenting signs and symptoms which may guide a health care professional; and
- the impact of the result (true or false) on the individual and/or public health (44).

Classification may differ between jurisdictions. For example, rapid diagnostic tests may be classified as Class B in one jurisdiction but as Class C in a country where a disease is endemic.46 In general, however, adherence to the internationally harmonized classification rules is encouraged.

Recategorization of medical devices may be appropriate as experience and knowledge about a device increase. The original categorization of a device may be changed through recategorization to a higher risk class when available scientific evidence shows that existing controls are not sufficient to assure the safety and performance of the device. Recategorization to a lower risk class may be acceptable if the available scientific evidence shows that less rigorous controls would provide reasonable assurance of the safety and performance of the device.47 General recategorization may be accomplished through revision of the classification rules if they are found to be deficient, thereby affecting a category of similar devices. Alternatively, an individual device may be recategorized by an evidence-based regulatory decision, without changing the general classification rules.

The NRA may develop explanatory guidance to help manufacturers apply the classification rules (47, 48).48 While the manufacturer has the primary obligation to categorize its medical device, its decision may be reviewed and challenged by the NRA. Table 4.1 shows illustrative examples of medical devices and their risk classes.

For IVDs, a four-class alphabetical system is recommended to identify the risk-based classes as shown in Table 4.2 (see section 4.4.1 below).

---

47 For example, see: https://www.fda.gov/about-fda/cdrh-transparency/reclassification, accessed 23 January 2023.
### Table 4.1
**Examples of medical devices by risk class**

<table>
<thead>
<tr>
<th>Class</th>
<th>Risk</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low</td>
<td>Examination gloves; patient hoists; stethoscopes; wheelchairs; surgical masks.</td>
</tr>
<tr>
<td>B</td>
<td>Low–moderate</td>
<td>Surgical gloves; infusion sets.</td>
</tr>
<tr>
<td>C</td>
<td>Moderate–high</td>
<td>Condoms – unless with spermicide (in which case, Class D); infusion pumps; neonatal incubators; therapeutic and diagnostic X-ray; lung ventilators; haemodialyzers; anaesthesia equipment.</td>
</tr>
<tr>
<td>D</td>
<td>High</td>
<td>Implantable cardioverter defibrillators; pacemakers; breast implants; cardiovascular stents; spinal needle.</td>
</tr>
</tbody>
</table>

### Table 4.2
**Examples of IVDs by risk class**

<table>
<thead>
<tr>
<th>Class</th>
<th>Risk level</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low individual risk and low public health risk</td>
<td>Clinical chemistry analyser; general culture media.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate individual risk and/or low public health risk</td>
<td>Vitamin B12; pregnancy self-testing; anti-nuclear antibody; urine test strips.</td>
</tr>
<tr>
<td>C</td>
<td>High individual risk and/or moderate public health risk</td>
<td>Blood glucose self-testing; HLA typing; PSA screening; rubella.</td>
</tr>
<tr>
<td>D</td>
<td>High individual risk and high public health risk</td>
<td>HIV blood donor screening; HIV/AIDS diagnosis.</td>
</tr>
</tbody>
</table>

---

49 The actual classification of each device will depend on the claims made by the manufacturer for its intended use and the technology or technologies it utilizes. As an aid to interpreting the purpose of each rule, illustrative examples of medical devices that should conform to the rule have been provided in Table 4.1. However, it must be emphasized that a manufacturer of such a device should not rely on it appearing as an example but should instead make an independent decision on classification taking into account its particular design and intended use.

50 The actual classification of each IVD depends on the claims made by the manufacturer for its intended use and the technology or technologies it utilizes. As an aid to interpreting the purpose of each rule, illustrative examples of IVDs that should conform to the rule have been provided in Table 4.2. However, it must be emphasized that a manufacturer of such an IVD should not rely on it appearing as an example but should instead make an independent decision on classification taking into account its particular design and intended use.
4.3 Principles of safety and performance

Regulations should specify that a medical device shall be safe and perform as intended by the manufacturer when placed on the market. IMDRF has established a list of essential principles of safety and performance for medical devices including IVDs (37, 49). These requirements have been widely adopted. The manufacturer shall demonstrate to the NRA that its product complies with these essential principles and has been designed and manufactured to be safe and perform as intended throughout a product’s life-cycle when used in accordance with the manufacturer’s intended purpose. The general essential principles apply to all medical devices and are supplemented by those principles specific to particular medical device types (for example, implants, electrically powered devices or IVDs).

The general essential principles of safety and performance for medical devices that apply to all devices include the following:

- The design and production processes should ensure that a medical device when used according to its intended purpose and by its intended user (lay person or professional) is safe and does not compromise the clinical condition of the patient or the health of the user.
- Medical devices should perform as the manufacturer intended when used under normal/specifed conditions.
- Each medical device including IVDs should also be accompanied by, or direct the user to, any safety and performance information relevant to the user or any other person, as appropriate.
- The manufacturer should perform a risk assessment to identify known and foreseeable risks and to mitigate these risks in the design, production and use of the medical device.
- The manufacturer should implement risk control measures to eliminate or appropriately reduce risks.
- Known and foreseeable risks should be weighed against the benefits of the intended purpose.
- Performance and safety should not be affected by transport or packaging and storage, provided the instructions for transport, packaging and storage are followed.

---

Beyond these general essential principles, further essential principles apply to some categories of medical devices, including principles related to the biocompatibility of materials, sterilization, electrical and mechanical safety, and software controls.

Ensuring and documenting that a medical device of any class conforms to all relevant essential principles (37) before placing it on the market is the responsibility of the manufacturer. The GMRF recommends that the NRA encourages manufacturers to apply recognized international consensus standards to demonstrate conformity with the essential principles of safety and performance. The manufacturer’s evidence of conformity, recorded in its technical documentation, may be subject to review by the NRA, either before or after market introduction (see Table 4.3). The medical device regulations shall specify the extent of the NRA’s pre-market evaluation of different classes of devices (20, 32, 44). While retaining responsibility for the decisions it makes, the NRA may appoint one or more conformity assessment bodies (CABs)52 to assist it in this task (see section 5.9 below).

The manufacturer is also responsible for ensuring that any changes to the intended purpose, design, specifications, labelling and/or manufacture of a device after its initial placing on the market also conform to the essential principles. Depending on the device classification, a further pre-market evaluation by the NRA of such changes may also be necessary.

4.3.1 Clinical evidence for non-IVD medical devices

Clinical evidence (17) is a component of the technical documentation of a medical device, which together with other design verification and validation documentation, device description, labelling, risk analysis and manufacturing information, is needed to allow a manufacturer to demonstrate conformity with the essential principles. One of the requirements of the essential principles is that “the device will perform as intended by the manufacturer and not compromise the clinical condition or the safety of patients”. Manufacturers should provide information on both the inherent risks and the benefits associated with using the device, and on the uncertainty associated with how accurately they can define the risks and benefits. Clinical evidence is important for demonstrating compliance with these requirements. In deciding whether to authorize a medical

---

52 Certain technical elements of the regulatory framework may be delegated to designated or recognized CABs. For example, they may be approved to perform initial certification and surveillance audits of a device manufacturer’s quality management system (QMS) and/or pre-market evaluation of device conformity with the essential principles. Satisfactory compliance with requirements is typically confirmed by the CAB issuing a design examination or QMS audit certificate. Based on the CAB’s evaluation, the NRA may make its final decision on compliance. The CAB performs its evaluation under the oversight of the NRA and may be subject to periodic assessments by that authority.
device, the NRA may consider the acceptance of data from clinical investigations conducted outside its jurisdiction, provided that the applicant has demonstrated that the data are adequate and were obtained in accordance with applicable global and national standards and in accordance with the characteristics of the population within the authority’s jurisdiction.

Some technologies have been available for many years and their clinical safety and performance have been well characterized. Many devices, however, utilize new technologies that have had little prior application in the diagnosis or treatment of humans and for which safety and clinical performance have not yet been established.

For long-established technologies, clinical investigation data that might be required for novel technologies may not be necessary. The available clinical data in the form of literature, (manufacturer’s) reports of clinical experience, reports of post-market experience (if applicable) and adverse event data for previous versions of the device may be adequate to establish the safety and performance of the device, provided that new risks have not been identified, and that the intended use(s)/purpose(s) has/have not changed. For high-risk devices with new design, material or software, new evidence would be needed. The manufacturer should perform a documented comprehensive clinical evaluation of all the available clinical data under the control of its QMS. The clinical evaluation report will become part of the technical documentation for the device and may serve as the basis for determining whether a new clinical investigation is appropriate. A widely used international standard for the practice of clinical investigation is ISO 14155:2020: Clinical investigation of medical devices for human subjects – Good clinical practice (18).

4.3.2 Assessing conformity to the essential principles

To a large extent the quality, safety and performance of a medical device, regardless of its classification, are determined by systematic controls applied by the manufacturer to its design, development, testing, manufacture and distribution, and use over the device’s life-cycle. In general, the manufacturer does this through implementation of a QMS, coupled with comprehensive technical documentation showing that the device conforms to the essential principles. The degree of assessment of the QMS by the NRA or CAB depends on the medical device risk class (Table 4.3). Depending on the class of the medical device, the evidence of conformity may be subject to regulatory assessment by the NRA or CAB (7, 20).
### Table 4.3
Conformity assessment processes as determined by device class

<table>
<thead>
<tr>
<th>Conformity assessment element</th>
<th>Class A</th>
<th>Class B</th>
<th>Class C</th>
<th>Class D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality management system (QMS)</td>
<td>Regulatory audit normally not required, except where assurance of sterility or accuracy of the measuring function is required.</td>
<td>The NRA should have confidence that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to market authorization.</td>
<td>The NRA should have confidence that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to market authorization.</td>
<td>The NRA should have confidence that a current and appropriate QMS is in place or otherwise conduct a QMS audit prior to market authorization.</td>
</tr>
<tr>
<td>Technical documentation</td>
<td>Pre-market submission normally not requested.</td>
<td>Not normally reviewed pre-market. The NRA may request and conduct a pre-market or post-market review sufficient to determine conformity with essential principles.</td>
<td>The NRA will undertake a review sufficient to determine conformity with essential principles prior to the device being placed on the market.</td>
<td>The NRA will undertake an in-depth review to determine conformity with essential principles, prior to the device being placed on the market.</td>
</tr>
<tr>
<td>Declaration of conformity</td>
<td>Submission normally not requested.</td>
<td>Review and verify compliance with requirements by the NRA.</td>
<td>Review and verify compliance with requirements by the NRA.</td>
<td>Review and verify compliance with requirements by the NRA.</td>
</tr>
</tbody>
</table>

---

53 There are many terms used to describe a product’s technical documentation. These include technical file, table of contents, standard technical documentation, design dossier, product design dossier, product summary file and product master file.
Class A medical devices, except those that are sterile or have a measuring function, are usually notified by the manufacturer to the NRA by listing (34) before being placed on the market. They are generally not subject to pre-market on-site QMS audits or routinely audited by the NRA after being placed on the market. Although Class A medical devices do not require pre-market submission of technical documentation, the manufacturer is required to retain technical documentation, along with a declaration of conformity, demonstrating conformity with the essential principles. The NRA may, at its discretion, require submission of a summary of the technical documentation and/or other evidence of conformity with the regulatory requirements.

For medical devices in all classes, the NRA or CAB shall have access to sufficient evidence to demonstrate the conformity of the manufacturing site(s) with the QMS requirements. For Class A devices, this would generally be on the basis of the manufacturer’s declaration of conformity. For Class C and D devices, clinical evidence should be submitted. The amount and detail of clinical evidence required depends on various factors. This evidence is not required for Class B devices, but manufacturers should have this information available upon request. For Class B and C devices, the NRA can generally rely upon assessments and audits conducted by a reference regulatory authority or CAB, when such audits have been conducted. For Class D devices, the NRA or CAB may supplement such reliance with its own QMS inspections or audits. The depth of the QMS audit is at the discretion of the NRA or CAB. In all cases, the NRA should retain the power and discretion to conduct its own QMS audits.

For Class C and D medical devices, the pre-market assessment usually includes a review of the summary technical documentation. This would typically comprise a device description, the essential principles checklist, the risk management file (risk management plan, risk assessment and risk management report) (50) on design and manufacturing, clinical evidence, product validation and verification, post-market surveillance plan and labelling. The NRA should specify whether summarized or detailed information should be submitted – for Class D devices, detailed information would typically be needed, while Class C devices may require only a summary of the technical information. For Class D devices, a QMS audit prior to market authorization is usually performed. The NRA could rely upon or recognize the work of a reference regulatory authority but the final responsibility lies with the NRA. For all classes of devices, the manufacturer should prepare, hold and be prepared to submit as required a declaration of conformity that the device complies fully with all regulatory requirements (20).

A regulatory pathway for medical devices according to risk class is described in section 7.1 below.
4.4 **Specific considerations for regulation of IVDs**

According to the GMRF, IVDs must comply with regulatory requirements similar to those for other medical devices. However, there are some differences that require consideration. This section discusses these differences and outlines steps to address them.

4.4.1 **Classification of IVDs**

As with other medical devices, risk-based classification provides a basis for allocating and prioritizing resources for the assessment of IVDs supplied in a particular market. There are a large number and variety of IVDs available, with varying impact on the diagnosis and management of patients. The risk presented by a particular device depends substantially on its intended use, indications for use and intended user. Regulatory controls should be proportionate to the level of risk associated with a medical device. The higher the risk associated with an IVD, the more stringent the assessment should be. Unlike other medical devices, the risk associated with an IVD is indirect and is related to the risk of incorrect diagnosis, disease staging, monitoring or surveillance for both the patient being examined and the population in general. For example, an undiagnosed patient with a serious infectious disease could put a whole community at risk.

The classification of an IVD is based on the following criteria:

- The intended use and indications for use as specified by the manufacturer.
- The technical/scientific/medical expertise of the intended user (lay person or health care professional).
- The importance of the information to the diagnosis (sole determinant or one of several), taking into consideration the natural history of the disease or disorder including presenting signs and symptoms which may guide a physician.
- The impact of the result (true or false) on the individual and/or public health.

An IMDRF classification scheme for IVDs has been published that includes classification rules based on risk to the individual and to public health (44). Software as a medical device (SaMD) that processes output from an IVD should be classified based on the SaMD’s intended diagnostic purpose (51).

The IMDRF IVD classes in ascending order of risk are:

- **A** – low individual risk and low public health risk
- **B** – moderate individual risk and/or low public health risk
• C – high individual risk and/or moderate public health risk
• D – high individual risk and high public health risk.

The importance of the result of the IVD in making a diagnosis is also a factor, with a higher risk class assigned where the IVD is the sole determinant in making a diagnosis.

4.4.2 Essential principles of safety and performance for IVDs

The IMDRF has developed additional essential principles that apply to IVDs (37). While the essential principles are similar in nature for each product type, the different conditions of use of IVDs require more specific wording in some cases and more detailed explanation in others.

The main differences are that the essential principles for IVDs:

• do not cover incorporation of substances considered to be a medicine, as even if these substances are present, there is no effect on the human body;
• place less emphasis on the need for veterinary controls on animals used as the source of biological material, as the risk of transmissible spongiform encephalopathy infection and other infections is reduced due to the mode of use of IVDs;
• include a requirement for the design to ensure that performance characteristics support the intended use;
• do not include requirements in relation to protection against ionizing radiation, since this is not a function of IVDs;
• have more limited requirements in relation to electrical safety and supply of energy, since IVDs do not connect to, or supply energy to, the patient;
• include requirements for IVDs for self-testing;
• include requirements for performance evaluation of the IVD (whereas clinical evaluation is appropriate for non-IVD medical devices); and
• include the requirement that values assigned to calibrators and controls of IVDs should be traceable to available reference measurement procedures and/or available reference materials of a higher order.54

In developing and implementing a regulatory system, jurisdictions are advised to adopt the IMDRF Essential principles of safety and performance of medical devices and IVD medical devices (37).

4.4.3 Clinical evidence for IVDs

As with medical devices in general, the clinical performance for an IVD is all the information that supports the scientific validity and performance for its use as intended by the manufacturer (12, 17). It is an important component of the technical documentation of an IVD, which together with other design validation and verification documentation, device description, labelling, risk management file (risk management plan, risk assessment, and risk management report) (50) and manufacturing information is needed to allow a manufacturer to demonstrate conformity with the essential principles (37, 52, 53). Clinical evidence includes analytical performance, clinical performance and clinical validity data.

A considerable amount of information on IVD performance is gained from analytical and clinical performance studies carried out on specimens obtained from human sources. This changes the risk profile of a clinical study as compared to clinical investigations for medical devices to be used on human patients. The application of ISO 14155:2020: Clinical investigation of medical devices for human subjects – Good clinical practice (18) is therefore not suited to IVDs. A standard specific to IVDs has been developed, namely ISO 20916: 2019: In vitro diagnostic medical devices – Clinical performance studies using specimens from human subjects – Good study practice (54).

4.4.4 Lot verification testing of IVDs

Countries may implement a system of risk-based lot verification of high-risk IVDs (Class D), either before distribution to users, post distribution or before they are put into service. The objective of lot verification testing is to verify that each lot supplied meets its safety, quality and performance requirements, and that transport and/or storage conditions have been well controlled so as not to affect the performance of the IVD. The need for lot verification testing depends upon the other controls in place in the importing country and the extent of pre-market evaluation conducted. Where there are stringent controls on transport and storage, and the receiving laboratory has in place an effective quality control programme that will detect problems in the performance of a new batch on arrival, lot verification testing may not be needed. The NRA may designate a national reference laboratory or other competent laboratory55 that is assigned

---

55 Competency is the capability to apply or use a set of related knowledge, skills and abilities required to successfully perform “critical work functions” or tasks in a defined work setting – see ISO 15189:2022 (84) for medical laboratories or ISO 17025:2017 (33) for other testing laboratories.
the overall responsibility for coordinating and conducting lot verification testing on its behalf.

5. Enabling conditions for effective regulation of medical devices including IVDs

Public confidence in medical devices including IVDs requires effective and efficient regulation built upon a sound legal and policy foundation, as well as GRP. The general principles provided in WHO Good regulatory practices in the regulation of medical products (4) should be applied when establishing a new – or revising an existing – system for regulating medical devices including IVDs. These principles include:

- legality
- consistency
- independence
- impartiality
- proportionality
- flexibility
- clarity
- efficiency
- transparency
- science based.

5.1 Legal requirements

Medical device regulations must have a sound basis in law. There is no single approach to the legal foundation of a regulatory framework as this will depend upon the national constitution and existing general national legal and administrative systems within the country. A generalized architecture of such a framework is shown in Fig. 5.1.
In all cases, the law should define the products within its scope and identify the entities subject to regulation. It should create a general requirement that only medical devices including IVDs that are safe, perform as intended and are of appropriate quality may be marketed or made available for use in the jurisdiction. The law should delineate the responsibilities of the NRA and establish its enforcement powers to include restricting the circulation of, or withdrawing products from, the market, as well as imposing penalties. It should establish mechanisms for ensuring the accountability of the executive, judicial and legislative branches of government (see also Appendix 1 below). It should address coordination with other government bodies such as the justice ministry, the police and customs authorities. In countries with decentralized systems, the respective powers and coordinating roles of the central regulatory authority and authorities in the political subunits will have to be defined.

The law should establish and define the responsibilities of manufacturers, authorized representatives, importers, exporters and distributors in the regulatory process. Where regulatory authority is delegated to an independent administrative agency there should be clear lines of political oversight and accountability – for example through the Ministry of Health. It should be clear to stakeholders which authority is responsible for what. The legal framework
should also provide scope for administrative and enforcement discretion and authorize the NRA to implement the principles of reliance and recognition within a set timeline (see section 5.9 below). This provision will ensure that the NRA implements an effective reliance and recognition pathway and leverages decisions, including but not limited to assessments and regulatory decisions made by authorities in other jurisdictions, CABs and trusted institutions such as WHO. The law should allow the NRA to establish approval pathways for specific circumstances and categories of devices – for example, donated medical devices, investigational use only and research-only products (that is, not intended for diagnostic use), emergency use authorization and personal use medical devices including IVDs. It should also allow the NRA to respond to public health emergencies in an appropriate and timely manner. The law should accommodate a transition period when new regulatory requirements are established and when moving from basic-level to expanded-level regulatory controls as resources allow and as experience is gained.

The NRA should adhere to GRP such as creating opportunities to obtain and review public comments on proposals, assessing regulatory impacts, allowing reasonable transition periods for stakeholders, and adopting requirements that are proportionate and offer the least burdensome ways of achieving policy goals. Regular interactions with stakeholders, including patient organizations, consumer groups and academic professional associations are key in obtaining support and commitment. Stakeholders should be consulted on the development of new laws and regulations in order to receive feedback and guidance on the proposed laws and regulations (see section 9.1 below). The provisions of laws, regulations and guidelines should be as transparent, predictable and internally consistent as possible. Measures should also be non-discriminatory, so that all similarly situated parties are treated in the same way and decisions taken without regard to the national or international origin of a medical device or to the source of financing or the sector of the health care system in which it is used – for example, whether primary, secondary, tertiary or emergency health care, or whether delivered through a public, private or military facility. The principles and enablers of GRP and components of a regulatory system are shown in Fig. 5.2.

5.2 Gap analysis of existing controls

It is important at an early stage of introducing a regulatory framework to evaluate any existing regulatory controls that apply to medical devices including IVDs. This will allow policy-makers to understand both the steps and resources needed to achieve national public health goals and to develop regulatory capacity. A gap analysis is helpful in assessing the degree to which national regulations are aligned with international guidance and best practices (4).
Fig. 5.2
Principles and enablers of GRP and components of a regulatory system (4)

Regulatory framework
1. Legal framework (laws & regulations)
2. Guidelines and other guidance documents

Resources
Human resources, financial resources, equipment, infrastructures, information management systems

Regulatory Institutions
National Regulatory Authority (NRA), National Control Laboratory (NCL), Pharmacovigilance center, Research Ethics Committee & others

Regulatory outputs
- e.g., inspection/assessment reports, regulatory decisions, approved product labeling/information

Regulatory outcomes
- e.g., increased compliance with regulatory requirements

Regulatory impact
- e.g., access to safe, effective and assured quality medical products, less substandard and falsified medical products on the market, increased pharmaceutical contribution to country’s economic revenues

GRP enablers
- Political and government support
- Good organization, governance and leadership
- Effective communication, collaboration & coordination
- Robust and well-functioning quality management system
- Sufficient and sustainable financial resources
- Competent human resources
- Pre-set organizational ethics and values
- Science and data driven regulatory decision making process

GRP principles
- Legality
- Consistency
- Independence
- Impartiality
- Proportionality
- Flexibility
- Clarity
- Efficiency
- Transparency
The NRA should conduct a gap analysis and seek the views of interested parties, including patient, health care sector and industry representatives. The results of the analysis will aid in setting priorities for implementation. For example, in a country with little or no domestic production, it may be appropriate to focus first on import controls, rather than on manufacturing controls. In a country with a high prevalence of sexually transmitted diseases, it may be prudent to give priority to regulatory controls for medical devices including IVDs used in the prevention, diagnosis and treatment of such diseases. Box 5.1 lists the elements to be considered in a gap analysis (55).

### Box 5.1

**Non-exhaustive list of elements to be considered in a gap analysis of medical device regulation**

- Are medical devices including IVDs regulated at all?
- Are they currently regulated as medicines or some other product category?
- Is there a specific and sound legal foundation for the regulation of medical devices including IVDs?
- Does the NRA observe GRP when drafting regulations?
- Has a regulatory impact analysis been performed?
- Is there a clear definition of the term “medical device” and does it match the definition recommended by this GMRF?  
  
56

- What are the public health risks that exist in the country, and can those risks be mitigated by the use of medical devices including IVDs?
- Is there a system of market authorization?
- Does the NRA use international standards and harmonization or benchmarks in its regulatory process?
- Does the NRA use reliance or recognition mechanisms in its regulatory process?
- Is there an NRA with clear powers and oversight for health products?
- Does the regulator have the proper competencies required for effective implementation and enforcement?
- Where there is a legal framework, is it enforced, and does the NRA have sufficient resources, expertise and funding to perform its duties?
- Does the NRA adopt codes of conduct to be observed by all its staff members?
- What proportion of medical devices including IVDs are imported and from where?
- Are there local manufacturers of medical devices including IVDs? If so, are their activities regulated, and how?

56 The definition used in this GMRF is taken from the GHTF (6) and from the IMDRF (37).
Box 5.1 continued

- Are all relevant stakeholders adequately represented in consultations?
- Are distributors and importers subject to appropriate controls?
- Is there evidence that substandard and falsified (SF) medical devices including IVDs have been placed on the market?
- Are there processes and procedures in place to prevent, detect and respond to SF medical devices including IVDs?
- Do existing laws and regulations comply with international good practices and treaty obligations?

5.3 Implementation plan

Once national legislation on medical devices including IVDs has been adopted, the appointed NRA should develop and publish a plan for its implementation. The plan will be driven by public health priorities and needs, and by the availability of resources, including trained competent staff to implement the legislation. Risk management should be an integral part of management and decision-making and be integrated into the structure, operations and processes of the organization. Risk management includes determining the scope, context and criteria that are relevant to the regulatory processes.

The elements subject to risk management for medical devices including IVDs can be derived from the WHO global benchmarking tool plus medical devices (GBT + medical devices) for evaluation of national regulatory systems of medical devices including in-vitro diagnostics – Revision VI (3) – namely, the national regulatory system, registration and market authorization, adverse event and incident reporting, market surveillance and control (including import controls), registration of establishments, regulatory inspections, laboratory testing and clinical trials oversight.

The implementation plan should include time for promoting awareness, drafting proposals for implementing regulations, and seeking feedback from the public and other affected parties. Appropriate transition periods should be defined to allow industry to comply with new or amended requirements. The plan should also address how medical devices including IVDs already on the market, in the distribution chain or in use will be handled – for example, through the allowing of well-defined exemptions and transition provisions. The NRA should hold meetings and publish guidance documents to ensure that medical device manufacturers, importers, distributors and purchasers are aware of their responsibilities, thereby avoiding disruption to the supply of medical devices including IVDs during the transition period.

A road map of actions, timelines and deliverables may be a useful tool during the implementation of the plan (see section 9.2 below) (56).
5.4 Monitoring implementation

At the time of development of the implementation plan, goals, regulatory processes, and performance-based indicators should be established to allow the progress of implementation to be assessed against a baseline of the current status of the legal framework for medical devices including IVDs. The WHO GBT + medical devices resource (3) provides the functions and indicators which enable regulatory authorities to establish their baseline in a systematic manner and to develop their institutional development plan. Progress should be reported to the legislature, parliament and the public, bearing in mind that the strategy, implementation plan and enforcement aims should be aligned with available resources. Such reports will help towards ensuring transparency and political accountability. They may also be used to evaluate the adequacy and use of resources. The progress made may also be used to help determine the timing of future steps in implementing the regulatory framework. A law with modest aims and objectives that is properly enforced is preferable to a more comprehensive one that cannot be implemented (4). If expanded-level regulatory controls are established, it may be appropriate to include performance measures such as timely response by the NRA in monitoring manufacturer responses to quality defects and/or serious injury associated with the use of their medical devices including IVDs. Other, more general, performance measures may include the holding of periodic consultations with interested parties such as medical device users, patient representative groups and industry. Ultimately, the public and parliament or legislature will want to see that their confidence in the NRA and its use of resources is justified.

5.5 National regulatory authority

Implementation of the medical device law will require the appointment of an NRA with the power to exercise independent decision-making within the legal framework. The NRA may be established either within an existing government department (such as the Ministry of Health) or as an independent administrative agency accountable to a ministry. The governance structure and mechanisms of the NRA should be defined, and appropriate checks and balances established, along with a requirement to publish periodic public reports on performance. In countries where the law (or decree) consists of statutes setting out broad outlines and principles only, it must delegate powers to the NRA to issue regulations (also known as statutory instruments or implementing acts), while specifying the substantive requirements and procedural regulations for implementing them. It should also provide the NRA with the necessary enforcement powers (see also Appendix 1 below).

While retaining in full the responsibilities placed upon it by the law, the NRA may designate CABs to assist it in carrying out some of its duties. In this
situation, the regulations will include the requirements for appointing a CAB, setting the scope of its responsibilities and monitoring its performance. Although the CAB may perform some evaluation functions under the supervision of the NRA, the final decisions and enforcement powers remain with the NRA.

5.6 Funding the regulatory system

Implementation of the regulatory system will require well-trained staff, infrastructure, facilities and information technology (IT). The resources allocated should be consistent with the responsibilities and activities mandated in the law, with a legal provision that allows for such resources to be increased as the regulatory system moves from basic-level to expanded-level regulatory controls. The pre-implementation gap analysis should include an assessment of the financial resources required. Consistent with its financial policies and legislative intent, a country may choose to fund all regulatory activities from public funds, or from a mixture of public funds and fees collected from the regulated industry (that is, user fees). If user fees are imposed, they should be predictable, transparent, non-discriminatory, reasonable in relation to the services rendered, and subject to periodic review. Permission for the NRA to impose fees for selected activities should be established through the medical devices law. One way for the NRA to increase efficiency and thereby reduce costs is to take into account the outputs (for example, reports and decisions) of regulatory authorities in other jurisdictions in reaching its own decisions (that is, reliance or recognition) as appropriate.

The costs of doing business – both direct costs (for example, user fees) and indirect costs (for example, the regulatory burden of compliance with local requirements) – may have an influence on whether medical devices including IVDs are introduced to a particular market. If the costs of compliance appear disproportionately high compared to the potential of a given market, or if regulatory requirements are not harmonized with those of other countries, manufacturers and importers may be discouraged from offering their products, which may in turn impede the achieving of national public health goals.

5.7 Conflict of interest and impartiality

Public confidence in the integrity of the NRA and its actions is essential. The authority and its staff, advisory committees and CABs should be seen to act consistently, impartially and transparently. Any actual or perceived lack of impartiality with regard to regulatory decisions could lead to unfair and unjust competitive advantages for parties in the medical device sector, as well as a lack of confidence in the medical devices including IVDs supplied to the market. This can be prevented by the adoption of, and consistent adherence to, a code of conduct by all members of staff. This code should provide a framework for decisions and actions and allow for public and legislative scrutiny of the NRA.
Staff must avoid situations where there may be a conflict, real or perceived, between their private interests and the public good. The NRA should establish a conflict-of-interest policy, avoid improper bias, be transparent in funding and base its decision-making on scientific criteria. Leaders within the organization must set the tone through the good example of their own conduct (4).

5.8 Regulatory competencies and resources

Regulating medical devices including IVDs effectively and efficiently and according to GRP requires appropriate individual expertise, reinforced by the institutional capacity of the NRA. General competencies for regulatory professionals include an understanding of public health principles, analytical and communication skills, information handling, and effective intervention and crisis management skills. These competencies are needed even where the NRA relies on or recognizes the regulatory decisions of reference regulatory authorities. Additional specific competencies include essential knowledge of the regulatory system for medical devices including IVDs, and awareness and understanding of the responsibilities of the NRA, the concepts of international standards and harmonization, and the importance of QMS, along with an understanding of a range of different device technologies and their applications.

For each stage of implementing the regulatory system, a sufficient transition period should be established. A transition period allows the NRA to ensure that it has sufficient qualified and trained staff, appropriate resources and adequate information systems for its increased responsibilities and functions. Any transition period should aim to avoid disruption to the supply of medical devices needed to treat or diagnose patients. The NRA will also require legal support to interpret its responsibilities under the law, particularly with respect to its monitoring, enforcement and safeguarding activities. In addition, IT and administrative resources will be required.

Basic-level regulatory controls will require general technical expertise on medical devices including IVDs – whereas expanded-level regulatory controls will require some regulatory staff to have more specific technical expertise in particular fields (57). As the regulatory system and its implementation become more comprehensive, additional resources will be required (58, 59). All regulatory staff within the NRA should have mandatory and core competencies appropriate for their level. As shown in Fig. 5.3, the WHO global competency framework (60) is modelled as follows: (a) mandatory competencies; (b) core competencies; and (c) occupation-specific competencies.

In view of the importance of the manufacturer’s QMS, the NRA should recruit and train staff members with experience in that field. Such staff may inspect or audit manufacturers, authorized representatives, importers and distributors. These skills should allow the NRA to provide appropriate oversight
and control throughout the life-cycle of the medical device (58). When elements of the regulatory framework are delegated to CABs (see section 6.3.1.2 below), authorities should have competent regulatory staff to assess compliance by the CAB with the relevant requirements (14, 61).

Fig. 5.3
The WHO global competency framework (60)

Given the diverse nature of medical devices including IVDs, the NRA should over time, and according to the priorities in regulating specific medical devices including IVDs, recruit technical staff with a variety of appropriate expertise (58, 59). Ensuring a career path, professional development and recognition of the value of regulating medical devices including IVDs as a profession, may all be important in recruiting and retaining staff.

Even for advanced or well-resourced regulatory authorities it is impractical to have all the required expertise in-house. Instead, an advisory committee(s) can be created consisting of independent experts in a variety of fields to advise in specific technical areas. The process of nominating advisers and creating advisory committees should be transparent and be made public. Particular attention must be paid to ensuring the impartiality of members,
avoidance of potential or actual conflicts of interest, and establishing procedures for the exchange of confidential information. The NRA remains responsible for the decision even when based on the advice of advisers. Performing an assessment of the NRA’s current regulatory competencies and capacities will provide insights into any gaps in technical knowledge, the regulatory system and related functions.

Further information can be obtained from the WHO global benchmarking tool (2) and from published IMDRF guidance on good regulatory review practices (59).

Based on the findings of the gap analysis, both the initial and ongoing training of regulators for medical devices including IVDs should be implemented according to a training plan (see section 9.3 below).

5.9  Reliance and recognition

Reliance, recognition and abridged assessment through WHO prequalification are facilitated by international regulatory convergence – a process of gradual alignment of regulatory requirements in different countries, regions or globally (5).

The law should establish to what extent the NRA may reasonably use the assessment outcomes of a reference regulatory authority, a CAB or trusted institution such as WHO when assessing whether a device conforms to national requirements. When regulations do not make explicit provision for the application of reliance, it may be adopted through interpretation of existing regulations – for example, during emergency situations. Reliance can be implemented through policy change, as long as it is broadly consistent with national legislation. If the application of reliance is prohibited, revision of the legislation to enable reliance should be considered within a reasonable timeframe.

Reliance may take many forms and reflect varying degrees of application in recognizing or taking account of the assessments, decisions or other authoritative information available from other authorities and institutions. For example, where a reference regulatory authority authorizes a medical device to be placed on its own market, the relying NRA may use this information, possibly supplemented with information from the manufacturer, to reach its own decision. When relying on a reference regulatory authority, a relying NRA should only request additional information from the manufacturer when required to meet legislative requirements. While reliance approaches are widely used for the initial authorization of medical devices, they may also be used for adverse event and incident reports, and for other post-authorization activities.

(for example, post-approval changes and inspections) given the substantial regulatory resources required to evaluate safety and post-approval changes during a product’s life-cycle. If an NRA has relied on a reference regulatory authority, CAB or trusted institution such as WHO for its initial approval, the use of similar reliance measures for post-approval changes and adverse event and incident reports is beneficial provided that the sameness of the product initially authorized is maintained.

Recognition may be seen as a special and more complete form of reliance whereby one NRA relies on the regulatory decisions of another reference regulatory authority, system or institution, thus reducing the need for additional regulatory assessment in reaching its own decision.

As shown in Fig. 5.4, the usual phases of reliance and recognition evolve from confidence-building (during which work-sharing and joint activities are undertaken) through to reliance on regulatory information from the reference regulatory authority, to unilateral or mutual recognition of a regulatory decision.

In considering whether to use either the reliance or recognition option in its own decision-making, the NRA must have a clear understanding of the regulatory system and requirements of the reference regulatory authority as applied to the device under review. The reference regulatory system upon which
an NRA relies – or which it recognizes – should be equivalent or superior to the NRA’s own regulatory system. That decision should be based on defined criteria such as those used to determine maturity level in the WHO global benchmarking tool (3) and specifically those related to medical devices. It should also take into consideration that reliance will refer to a specific element of the regulatory process while recognition is the overall acceptance of the regulatory decision of the reference regulatory authority.58 For example, medical device regulations in some jurisdictions permit a manufacturer to specify some medical devices as “export only” and allow such medical devices to be subjected to only minimal controls rather than full evaluation of their conformity to national regulatory requirements.59 This places responsibility on the NRA of the importing country and may make reliance and recognition inappropriate. Reliance and recognition are also not appropriate for the assessment of specific requirements, such as language of labelling and electrical supply, that do not apply in the exporting country.

Medical devices may also have different configurations (regulatory versions) for different markets. These may vary in aspects such as intended use, site of manufacture, risk class, power supply, labelling language and applied quality control, among others. It is therefore important to ensure that when relying on assessment outcomes by entities in other jurisdictions that the regulatory version is the same60 as the product being proposed for placing on the market. Specifically, for IVDs, the use of reliance or recognition as mechanisms for market authorization is complex. This is because of the variation in classification of IVDs in existing regulatory systems (which determines the level of regulatory scrutiny) or because of newly accepted regulations in some jurisdictions. For example, the current European regulation on IVDs – Regulation (EU) 2017/746 (62) – replaced the IVD directive EU IVD Directive 98/79/EC. The new Regulation came into force in May 2017 with a transition period until 2025.61 As a result, IVDs on the market during the transition period (and for some years after that) may be subject to two substantially different regulatory frameworks. This example clearly illustrates why knowledge of the regulatory system upon which reliance or recognition is based is crucial.

58 In addition to the description provided in the Terminology section of this document, in the context of medical devices a “reference regulatory authority” is a trusted authority or institution that is competent and efficient in its performance with regard to medical device and IVD regulation and oversight.

59 Such double standards, whereby some jurisdictions set lower requirements for use in other jurisdictions, are considered to be unacceptable.

60 Sameness of product means that two products have identical essential characteristics (that is, the product being submitted to the relying authority and the product approved by the reference regulatory authority should be essentially the same) (5).

All regulations are subject to occasional revision that could affect the applicability of the reliance or recognition procedure. Importing countries must therefore be alert to any such plans in the exporting jurisdiction and take them into account when relying upon or recognizing a regulatory decision of that jurisdiction. In general, where an NRA seeks to rely upon information from a counterpart in another jurisdiction, it must first establish confidence in the counterpart authority and, if applicable, reach agreement on the exchange of confidential information. The same considerations apply to the outsourcing of any activities, for example to CABs (63) or experts (locally or internationally based). An example of a specific pathway in reliance is the collaborative registration procedure (CRP) abridged assessment (see section 8.8 below). In this case, the relying NRA takes into account the output of work performed by reference regulatory authorities, while performing only a limited assessment of the technical dossier – for example, with regard to labelling, stability or other country-specific requirements. This may also extend to the assessment of post-market changes to the medical device. The rationale is that prior stringent assessment provides assurance of quality, safety and performance. This approach therefore relies on the assessment of documentary evidence produced by a reference regulatory authority or WHO.

5.9.1 National responsibilities

There are certain regulatory activities that, due to their nature, fall only within the responsibility of the NRA. Examples include: (a) import controls; (b) the registration of domestic manufacturers, importers, distributors and authorized representatives; (c) handling reports of adverse events and incidents occurring in or affecting the domestic market; (d) market surveillance activities; (e) communication and monitoring of field safety corrective actions (FSCA); and (f) market withdrawals. Information sharing on adverse events and incidents and on any FSCA, as well as on market surveillance, is important. Although these regulatory activities should principally be performed by the responsible NRA, international collaboration and reliance approaches (for example, work-sharing) can also be beneficial in facilitating these activities.

---


63 Abridged regulatory pathways are regulatory procedures facilitated by reliance, whereby a regulatory decision is solely or partially based on application of reliance (5).

64 The CRP provides unredacted reports on the assessment, inspection and performance evaluation (in the case of in vitro diagnostics) upon request (and with the consent of the manufacturer) to participating NRAs (5).
5.9.2 **International collaboration**

Where resources permit, the NRA should participate in formal and informal information-sharing networks with other regulatory authorities. This will also facilitate confidence-building, with the possibility of work-sharing and reliance upon other regulatory authorities. International collaboration facilitates the exchange of information on regulating medical devices, and expedites prompt contact in the case of a serious public health threat.

### 6. Establishing a stepwise approach to regulating medical devices

6.1 **Stepwise approach**

This GMRF recommends establishing a regulatory system for medical devices taking a stepwise approach – from basic-level to expanded-level regulatory controls. The basic-level regulatory controls will form the foundation of the expanded-level regulatory controls. In addition, building a risk-based regulatory system requires a solid legal foundation (see section 5.1 above). The regulatory framework must also be sustainable and expandable, and able to accommodate advances in clinical practices, public health needs and evolving technologies. In order to promote international regulatory convergence and harmonization, this GMRF encourages countries to adopt the principles and elements recommended in internationally harmonized technical guidance into their legislation (64, 65).

Basic-level and expanded-level regulatory controls fall into three broad groups:

- those applied before a medical device is placed on the market
- those applied when placing the device on the market
- those applied after the device has been placed on the market.

The stepwise approach will allow the NRA to respond to national public health priorities and to progressively develop the capacities, knowledge and experience required. This approach will also help the NRA determine the resources needed for further implementation. Without effective implementation of the basic-level regulatory controls as a foundation, the elements of expanded-level regulatory controls will be of limited value and difficult to manage effectively.

Initially, the NRA may reduce the demands on its own resources and staff by either relying upon or recognizing the work or decisions made by other regulatory authorities or trusted institutions such as WHO. Resources may then be directed to post-market controls, which are the responsibility of the NRA. Furthermore, the NRA will indirectly gain knowledge of the regulatory status in other jurisdictions of devices placed on its own national market. The
implementation of expanded-level pre-market regulatory controls does not mean that a regulator should discontinue existing regulatory reliance practices. As an NRA subsequently implements such expanded controls, emphasis will shift to pre-market controls such as authorizing devices to be placed on the market, while continuing to rely upon or recognize the work of other NRAs or trusted institutions, where appropriate.

6.2 Basic-level regulatory controls and their enforcement

This GMRF recommends that the basic-level regulatory controls shown in Table 6.1 are incorporated into a medical devices law that determines the scope of regulation, stipulates the responsibilities of the NRA, describes the conditions under which a medical device may be placed on the market, requires parties that place medical devices on the market to register their establishments, establishes import controls, and requires the listing of medical devices placed on the market. Typically, the market surveillance activities of the NRA would include establishing a system for reporting adverse events and incidents to the NRA and ensuring that manufacturers have in place systems for taking appropriate action in response to reports of quality, safety or performance problems associated with the use of a medical device.

6.2.1 Publish law including definitions and regulations with transition period

The national law for medical devices will set out principles and broad requirements and delegate authority to the NRA (see section 5.1 above). In particular it will include provisions that:

- define the products and parties within its scope, in particular the terms “medical device” and “IVD”, using harmonized definitions (6, 37);
- ensure the regulatory framework is capable of adapting to new technologies and treatment modalities;
- designate the NRA, its enforcement powers, market oversight responsibilities, powers to issue implementing regulations, responsibility for publishing guidance documents to aid understanding of legal requirements, and the requirement to take action where the health of patients or users is compromised;
- provide the NRA with administrative discretion for reliance upon and recognition of the work or decisions of reference regulatory authorities in other jurisdictions (see section 5.9 above);
- require that only safe medical devices of good quality that perform as the manufacturer intends may be placed on the market;
- specify the market entry requirements for medical devices;
- establish record-keeping and reporting requirements for all parties within the scope of the law;
- create the option to appeal regulatory decisions;
- specify a transition period sufficient to allow parties affected by the law to comply with its requirements, and to ensure minimal disruption to the continuing supply of medical devices to health facilities and other users;
- specify that after the transition period, manufacturers shall comply with the regulatory requirements; and
- specify regulatory approaches during special situations such as public health emergencies.

To allow for progressive adoption and implementation of the stepwise approach recommended in this GMRF, the law should foresee and include provisions covering the expanded level of regulatory control and enforcement, even though those provisions would not likely be implemented in the early stages.

Experience in many jurisdictions with established regulatory systems suggests that stakeholders must be allowed time (that is, a transition period) to adapt to the law. In some situations, an extension of the transition period is required. In this case, the changes should be announced in advance and explanations should be published regarding the new transitional period. The length of the transition period will reflect the number of stakeholders potentially affected and the number of devices on the national market. It may be helpful to first establish new requirements on a voluntary basis, gain experience and then move to mandatory compliance. An important role of the NRA during the transition period will be the development and dissemination of voluntary guidance documents to stakeholders.

6.2.1.1 Establish medical device classification for regulatory purposes

The law should include a medical devices classification scheme, based on internationally harmonized guidance, to provide an efficient way of regulating each medical device according to its risk class (32, 44). It should also include provisions for the NRA to issue implementing acts and guidance on the classification of medical devices including IVDs. The manufacturer would then determine the risk class of a medical device based on the classification rules established by the NRA. Its decision may be challenged by the NRA during review and evaluation of the application for market approval, or at any time for Class A devices that do not require pre-market authorization. It is recommended that the NRA establishes a voluntary consultation process whereby manufacturers can ask for regulatory review of the proposed classification of a device (see sections 4.2 and 4.4 above).
Table 6.1
Basic-level regulatory controls and enforcement for medical devices within the legal framework

<table>
<thead>
<tr>
<th>Pre-market</th>
<th>Placing on the market</th>
<th>Post-market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publish law including definitions and regulations with transition period</td>
<td>Registration of establishments</td>
<td>Establish a system for reporting adverse events and incidents</td>
</tr>
<tr>
<td>Establish medical device classification for regulatory purposes</td>
<td>Listing of medical devices</td>
<td>Require mandatory notification by the manufacturer of field safety corrective actions</td>
</tr>
<tr>
<td>Establish Essential Principles of safety and performance</td>
<td>Import controls</td>
<td>Establish a procedure to cancel market authorization for products that no longer meet quality, safety or performance requirements</td>
</tr>
<tr>
<td>Establish basis for reliance and recognition</td>
<td></td>
<td>Establish a procedure to issue safety alerts to users</td>
</tr>
<tr>
<td>Establish requirements for Declaration of Conformity</td>
<td></td>
<td>Undertake market surveillance</td>
</tr>
<tr>
<td>Establish requirements for manufacturers for Quality Management System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Establish requirements for labels and labelling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prohibit deceptive, misleading and false advertising</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Establish provisions for exceptional pre-market situations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

65 Expanded-level regulatory controls are discussed in section 6.3 below.
6.2.1.2 Establish essential principles of safety and performance

The law should also establish the fundamental requirement that all medical devices are shown to be safe, perform as intended and are of good quality before they are placed on the market. This would require the manufacturer, or its authorized representative or importer, to declare, and be prepared to provide timely evidence showing, that their device is in compliance with the essential principles (see sections 4.3 and 4.4 above) (37). Failure to make such a declaration of conformity (see section 6.2.2.2 below) (20), or making a false declaration, would be grounds for enforcement action by the NRA.

The preferred way in which the manufacturer may demonstrate conformity with the essential principles is to apply voluntary international standards that are appropriate and relevant. The law should include provisions allowing the NRA to formally recognize such standards⁶⁶ for that purpose (see section 6.3.1.3 below).

6.2.2 Basic-level regulatory controls and enforcement – pre-market

Basic-level regulatory controls are intended to provide assurance that only medical devices that are safe, perform as intended and are of good quality are placed on the national market and put into service. Measures including the identification of manufacturers, authorized representatives, importers and distributors, as well as the listing of the medical devices they handle, are intended to provide tools that the NRA may use in enforcing regulatory requirements.

6.2.2.1 Establish a basis for reliance and recognition

The medical devices law should allow reliance and recognition practices to be used by the NRA in evaluating and determining whether a medical device complies with the regulatory requirements for placement on the domestic market. Nonetheless, the NRA is ultimately responsible for determining whether a medical device may be supplied in its jurisdiction (5).

6.2.2.2 Establish requirements for declaration of conformity

The medical devices law should require a manufacturer or any other natural or legal person seeking to place a medical device on the market to draw up, hold and, as required, submit or make available a written declaration of conformity attesting that the device complies fully with the law and all regulatory requirements.

At a minimum, this declaration should contain the following:

---

⁶⁶ Standards indicated in this document were current at the time of publication. Users should refer directly to the standards body to verify the currently used standards.
• The name and address of the natural or legal person with responsibility for the design and/or manufacture of a medical device with the intention of making the medical device available for use under its name.
• The regulation(s) under which the declaration is being made.
• A description of the device and its classification according to the regulation(s).
• A declaration that the medical device is of good quality, is safe and will perform as intended during its life-cycle when used for its intended purpose as stated in the instructions for use (IFU).
• Sufficient information to identify the device(s) to which the declaration of conformity applies.
• The list of standards used to demonstrate compliance with the relevant essential principles.
• The name, position and signature of the responsible person who has completed the declaration on the manufacturer’s behalf.
• The date on which the declaration is made.

The NRA should have the power to verify the declaration of conformity at any time, pre- or post-market, including at the point of importation – either as part of routine market surveillance or “for cause” in the case of suspected non-conformity. That verification process may include examination of supporting evidence from the manufacturer’s technical documentation.

6.2.2.3 Establish requirement for manufacturers to have a QMS
To ensure that devices are designed and manufactured to meet safety, performance and quality requirements during their life-cycle, the law should require manufacturers of all classes of medical devices to establish and maintain a QMS and associated records. The QMS should be appropriate to the specific characteristics of the manufacturer’s processes and products. This GMRF recommends that the QMS requirements should be aligned with the specifications in ISO 13485:2016: Medical devices – Quality management systems – Requirements for regulatory purposes (41) and ISO 14971:2019: Medical devices – Application of risk management to medical devices (50).67

The QMS is important not only for systematically assuring the quality, safety and performance of a device during its life-cycle but also for controlling the collection of technical evidence used by the manufacturer in preparing the declaration of conformity (see section 6.2.2.2 above).

---

67 In all cases, the latest version of an ISO standard should be applied.
6.2.2.4 Establish requirements for labels and labelling

The safe and effective use of most medical devices requires that the user be given information on how to use them properly and, where appropriate, on how to install, maintain and dispose of them. Information on intended purpose and proper use, contraindications, precautions and warnings should be provided. Labels, IFU and other labelling (for example, displays, service manuals and information for patients provided through web applications) serve that purpose and help to reduce the risks associated with the use of medical devices. The law should include a requirement that labels and labelling are appropriate to the intended user of a device, especially for lay persons, and should set language(s) requirements. To begin establishing regulatory controls, regulatory authorities must provide specific guidance on the labelling and language requirements for medical devices and fully describe any exceptions to these requirements. Regulatory authorities should ensure that labelling is in an official language or in a language acceptable for the jurisdiction. The NRA should also consider whether the IFU may be provided in addition to or instead of the printed instructions in alternative media, for example, via the internet or connected devices. However, printed IFU shall be provided if requested by the user and be provided for medical devices for use at home.

Labels should allow the identification of medical devices, for example by batch or lot number, or serial number. This will allow traceability by users to facilitate FSCA and help in the reporting and investigating of adverse events and incidents. One recent development has been the addition of internationally harmonized unique device identification (UDI) data on the label to identify the medical device both in human- and machine-readable form (see section 6.3.1.5 below).

Guidance may be provided by the NRA indicating whether specific information, for example authorized representative, establishment registration, specific markings and/or environmental information, could be made available via electronic media (e-labelling) (31).

A label (or labels) showing the identity and location of the manufacturer and, where applicable, distributor, authorized representative and/or importer should be provided on medical devices or on their outer packaging. This must be consistent with the information shown in the establishment registration. More detailed and specific information may be made available through e-labelling. Country-specific requirements for the label format or labelling information should be kept to the least-burdensome minimum. Where possible, the NRA should allow such information to be made available through electronic means.

6.2.5 Prohibit deceptive, misleading and false advertising

In addition to the requirements for labelling of medical devices, consideration should be given to provisions and prohibitions regarding the advertising and promotion of medical devices, including explicit enforcement measures. The NRA should issue clear and detailed guidance, including on the use of recognized international labelling standards and symbols. The NRA should ensure that promotion, including online promotion:

- does not target inappropriate audiences;
- makes only claims that are supported by evidence;
- covers only medical devices that have been authorized for placing on the market;
- is consistent with intended use and other information in the product labelling; and
- does not make false or misleading claims.

As a basic-level regulatory control, the NRA should investigate any suspected violations brought to its attention. If the NRA discovers that a requirement has been breached, it shall take appropriate enforcement actions, which could include correcting advertising materials or preventing the medical device from being placed on the market.

6.2.6 Establish provisions for exceptional pre-market situations

In situations such as public health emergencies, or for individual patients in exceptional circumstances, exemptions from some regulatory requirements may be appropriate. Such exemptions should, however, be applied in such a way as to allow the NRA to evaluate the risks and benefits of the specific situation and to authorize the proposed deviation. Such exemptions should be clearly stipulated and communicated to the stakeholder(s).

The law should establish defined exemptions from, and provide enforcement discretion for, compliance with certain requirements – for example, with regard to medical devices for humanitarian use, public health emergencies, clinical investigations and exhibition use, or medical devices donated to the country by charities or the manufacturer. Regulators should issue clear guidance on such exemptions (see section 5.1 above and section 7.3 below).

6.2.3 Basic-level regulatory controls and enforcement – placing on the market

Many countries depend almost entirely on imported medical devices. However, it is impractical for a medical device manufacturer to have a physical or legal presence in every country. Therefore, the law should require a manufacturer
outside the jurisdiction of the country concerned to appoint an authorized representative within the country (15, 66).

6.2.3.1 Registration of establishments

A key element of basic-level regulatory control is effective oversight of medical devices placed on the domestic market and of the parties responsible for bringing such devices to the market. The law should require local manufacturers, authorized representatives, importers and distributors (in some cases the authorized representative may also be the importer and/or distributor) who place medical devices on the market or make medical devices available for use in the jurisdiction to register with the NRA. Significant changes in a registered establishment (for example, changes in ownership, location, name of the responsible person or scope of activities) should be notified to the authorities in a timely manner to ensure that registration information is up to date and correct. Establishment registration is also useful in facilitating regulatory actions such as compliance inspections (for example, of warehouses or manufacturing plants), and notifying and monitoring of FSCA, as well as law enforcement actions. Making information on the registration of establishments and the listing of medical devices publicly accessible allows device purchasers or users to identify products available to them and to determine the identity and location of manufacturers and/or distributors, exporters and/or importers. It is the responsibility of the NRA to periodically check the validity of the registration information and to determine the interval for these checks (34).

6.2.3.1.1 Authorized representatives

The minimum requirements for registration of establishments should be that the authorized representative provides the NRA with information on its place of business, the name and position of a responsible person, contact information and the manufacturer(s) it represents. Additionally, the regulation may require the authorized representative to attest that it will act on behalf of the manufacturer in its dealings with the NRA by:

- submitting a listing (34) of medical devices placed on the domestic market and keep the list updated by notifying the NRA of any renewals or withdrawals;
- providing the NRA with the information it requires when the manufacturer seeks authorization to market its device(s);
- informing the manufacturer of all user feedback on adverse events, incidents and complaints related to safety and performance – in certain jurisdictions, the authorized representative may also be responsible for reporting adverse events and incidents to the NRA
within the local market, and ensuring that users (for example, health care facilities and pharmacies) act on any FSCA initiated by the manufacturer;

- reporting, in certain jurisdictions, an FSCA to the regulator on behalf of the manufacturer;
- cooperating with the manufacturer’s importers and distributors;
- ensuring training is provided to users by the distributor, manufacturer or third party, according to the manufacturer’s requirements; and
- cooperating with the NRA and providing it with any information it requires during market surveillance activities (11).

6.2.3.1.2 Importers and distributors

The minimum requirement for any person/entity to engage in the importation or distribution of medical devices should be that they are registered with the NRA. Beyond this, the regulation may require the importer or distributor to attest that it will at a minimum:

- ensure the medical devices it imports or distributes comply with safety and performance requirements, and are accompanied by the proper documentation including labelling information (for example, IFU and labels);
- ensure that all information, user feedback on adverse events and incidents, and any complaints related to safety and performance received from its clients or customers, is brought to the attention of the manufacturer/authorized representative, as appropriate;
- trace medical devices through that part of the supply chain with which it is directly involved; and
- comply with the manufacturer’s requirements for the storage, handling, transport and, as appropriate, maintenance of medical devices.

If the device manufacturer appoints its importer or distributor to also act as its authorized representative, there should be a separate registration for each activity (34, 66).

6.2.3.2 Listing of medical devices

The NRA should establish an information system and a requirement for manufacturers, authorized representatives, and importers and distributors to submit a listing of medical devices when placed on the national market, and
to periodically ensure that the listing information is up to date (34). Among other elements, the listing should provide the standardized generic descriptive names of the medical devices, where possible using an internationally recognized nomenclature (see section 6.3.1.4 below). Listing of medical devices will allow the NRA to determine which products are placed on the market and by whom. The NRA should specify the information set to be submitted for listing purposes. The information shall be consistent with that shown in the technical documentation of the medical device. In the event of a suspected problem with a medical device, listing also allows the NRA to contact the parties responsible for that product. The NRA should also have a means (such as an internet portal) of providing information to other parties, upon request, on medical devices legally placed on the market. Listing is not of itself equivalent to, or evidence of, a market authorization.

6.2.3.3 Import controls

In addition to the basic-level regulatory controls of registering establishments and listing marketed medical devices, import controls and documents such as QMS certificates, proof of market authorization in the exporting country, declaration of conformity and test reports may be appropriate. These controls and documents may include approval of importation documents by the NRA before shipment, and verification of imported products, either at the port of entry or at the importer’s premises. Knowing in advance what medical devices are to be imported provides an opportunity for regulators to verify whether the medical device has previously been listed and marketed in the country. It also allows for a review of evidence of compliance with regulatory requirements. The NRA determines which categories or risk classes of medical devices would require additional import controls. Collection of samples may be required in the case of suspected SF medical devices including IVDs. Inspection and/or panel testing, based on product risk, may also be required (for example, lot verification testing for IVDs – see section 4.4.4 above). Once the systems for the registration of establishments and listing of devices become mature, the imposition of these additional import controls may no longer be necessary.

There should be mechanisms put in place for cooperation between the NRA and other government bodies so that customs service and other relevant government officials can receive appropriate training in applying medical-device-specific rules (for example, on labelling). Medical devices should not be released by customs officials from the port of entry unless there is proof that the NRA has authorized them to be placed on the market. The NRA shall be equipped with enforcement powers to prevent medical devices that do not comply with regulatory requirements from entering the country. It may be helpful to designate official ports of entry for medical devices so that the NRA may better focus its resources and enforcement activities.
6.2.4 Basic-level regulatory controls – post-market

Medical devices may not always perform as expected. This may indicate potential problems in their design, manufacture, labelling, storage or distribution, handling or use. It could also reflect inappropriate device selection, installation, use or maintenance.

6.2.4.1 Establish a system for adverse event and incident reporting including serious public health threats

At the basic level, the NRA should establish a system whereby users, patients and the manufacturer of medical devices (either directly or through their authorized representative) can report adverse events and incidents, and submit user feedback (including complaints) regarding medical devices. Manufacturers should be obliged to report to the NRA if any of the following events associated with the use of their medical device occur within their jurisdiction:

- discovery of a serious public health threat;
- death, serious deterioration in the state of health of a patient, user or other person; or
- no death or serious deterioration in health of a user, patient/client or other person but the failure, malfunction, improper or inadequate design, manufacture, labelling or user error of the medical device that could lead to death or serious deterioration in the health of a user, patient/client or other person (11).

For IVDs, the risk of harm is usually indirect as the device itself is not used on the body. However, in view of the potential hazard to public health, any false-negative test result for Class D IVDs is reportable. To expedite the review of reportable events, it is recommended that the user or health care provider report such incidents directly to the manufacturer or, in the case of a non-domestic company, to the authorized representative. Reports of adverse events received by the NRA from health care professionals, patients or end-users, or obtained during regulatory inspections, must be passed on to the device manufacturer or the authorized representative for investigation and trend analysis. The manufacturer or its authorized representative should inform the NRA of the outcome of its investigation. If necessary, it should take steps such as an FSCA or the issuing of a field safety notice (FSN). The NRA may also conduct its own risk assessment. NRAs should exchange information with other NRAs if they find any indication that the use a medical device may have led (or is highly likely to lead) to a serious public health threat or that may affect other jurisdictions (26).

This process can be used to exchange early information on significant concerns or potential trends that individual regulatory authorities have observed, but that have not yet resulted in an FSCA.
6.2.4.2 Require mandatory notification by the manufacturer of FSCA

The law should require a manufacturer, either directly or through its authorized representative, to report to the NRA in a timely manner any FSCA it is undertaking in the country. If an NRA learns, either through its own market surveillance or through information exchange with other NRAs or manufacturers, of any newly identified potential hazard associated with a device, it should have an established procedure for issuing information notices to users, along with a publicly accessible repository (such as a website) for these notices. Such a system should also, in addition to the FSN sent by the manufacturer, allow for the targeting of specific parties, usually in consultation with health care professionals, so that they may act appropriately to protect public health and prevent unnecessary concern or confusion among medical device users or patients who are not affected. Communications should be appropriate with regard to both the intended recipients and the urgency of the action. The NRA should have in place means by which the effectiveness of corrective or remedial actions by the manufacturer or its authorized representative shall be monitored. The NRA should also be prepared to respond to questions from the public, clinicians, media and the government, and to exchange information with authorities in other jurisdictions.

6.2.4.3 Establish a procedure to withdraw unsafe medical devices from the market

NRAs have an obligation to enforce laws and regulations on medical devices to ensure that the public is protected from non-compliant, unsafe or SF products. Regulators are required to monitor compliance with requirements by registered manufacturers, importers, authorized representatives and distributors, and to take appropriate action when the NRA believes that public health has been put at risk, while also informing the public of this action through appropriate means.

Various approaches to enforcing regulations may be used – for example: (a) suspension or withdrawal of registration of local manufacturers, authorized representatives, importers or distributors; (b) withdrawal from the list of marketed medical devices; and (c) quarantine and disposal of medical devices. Manufacturers may be required to review the technical documentation and to revise labelling information (including precautions and warnings), especially for products that have been found to be associated with unforeseen harm and the labelling shown to be inadequate. Enforcement may also include the issuance of public alerts, warning letters, prosecution and financial penalties. Manufacturers often possess additional information regarding perceived safety issues. By requesting such information, and consulting with the manufacturer (and possibly with external advisers; see section 5.8 above) before issuing a public alert, the regulator can more thoroughly investigate the issue and provide important context in the alert. While the NRA’s primary responsibility is for the health of its own citizens, where it believes that an imported medical device is
unsafe or of poor quality, it should consider sharing its opinion with the NRA or CAB responsible for auditing the device manufacturer’s QMS, for the purpose of preventing identical devices being exported to other markets.

For SF devices, the enforcement of medical device regulations will often depend not only on the resources of the NRA itself, but also on effective collaboration with other bodies and groups. These may include regulatory authorities from other jurisdictions, customs officials, law enforcement and the judiciary, manufacturers, and user and patient groups.

6.2.4.4 Establish a procedure for issuing safety alerts to users
Although the manufacturer, directly or through its authorized representative, would typically have primary responsibility for notifying users of problems with a medical device, this GMRF recommends that the NRA establish a procedure for directly notifying health care facilities and other users of the affected medical device through the issuing of safety alerts. Where possible, the text of any such alerts should be discussed with the manufacturer or its authorized representative, but the final decision lies with the NRA.

6.2.4.5 Undertake market surveillance (see section 6.3.3.2 below)
Market surveillance is the NRA activity related to the oversight of medical devices on the domestic market. Market surveillance activities should be prioritized using a risk-based approach. The NRA may undertake targeted activities based on a risk assessment of the distribution chain, evaluation of user feedback (on the safety, quality and performance of devices) and/or information received from the post-market surveillance systems of medical device manufacturers and their authorized representatives.

6.3 Expanded-level regulatory controls and their enforcement
Once the basic-level regulatory controls have been implemented effectively and efficiently, the regulatory authority may consider implementing more advanced controls. To do so: (a) the law should provide the legal basis for such expanded-level regulatory controls; (b) the regulatory authority must have effectively enforced the basic-level regulatory controls; and (c) additional resources (including financing and technical expertise) must be available for this purpose. Building on the basic-level regulatory controls, the expanded-level regulatory controls are intended to be more comprehensive. In adopting such expanded controls, the regulatory authority may choose to implement one or more of the controls described below, according to the priorities of the country. As with basic-level regulatory controls, a stepwise approach should be taken when implementing the individual elements of expanded controls.
(Table 6.2) and this will be dependent upon the available technical expertise and other resources. Implementation should always be consistent with available resources – enacting and enforcing a limited set of requirements is preferable to attempting to implement a larger range of regulatory controls in the absence of proper enforcement (4).

Table 6.2
Expanded-level regulatory controls and enforcement for medical devices within the legal framework

<table>
<thead>
<tr>
<th>Pre-market</th>
<th>Placing on the market</th>
<th>Post-market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Create oversight of clinical investigation</td>
<td>Perform in-country quality management systems audits</td>
<td>Establish processes for review of manufacturer’s post-market surveillance</td>
</tr>
<tr>
<td>Appoint and have oversight of conformity assessment bodies (CAB)</td>
<td>Perform review of submissions for compliance with Essential Principles</td>
<td>Require mandatory and timely reporting of adverse events and incidents by manufacturers</td>
</tr>
<tr>
<td>Adopt standards</td>
<td></td>
<td>Inspection of registered establishments</td>
</tr>
<tr>
<td>Adopt medical device nomenclature system</td>
<td></td>
<td>Provide for testing laboratories</td>
</tr>
<tr>
<td>Control advertising and promotion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


The empty boxes shown in Table 6.2 indicate the option for an NRA to tailor its activities based on national priorities.

6.3.1 Expanded-level regulatory controls – pre-market

6.3.1.1 Create oversight of clinical investigations

The general essential principles established for basic-level regulatory controls (see section 4.3 above) includes the requirement that a device must be shown to be safe and perform as intended before being placed on the market. To fulfil this requirement, the manufacturer must maintain and be able to present evidence (including clinical evidence along with a clinical evaluation) of clinical safety and performance in the summary technical documentation (16–18). Such clinical evidence may (but does not necessarily) include the results of clinical investigations of that specific device. Where required as a part of the assessment of the technical documentation, the NRA or CAB will evaluate the adequacy of that clinical evidence and its evaluation (17, 67). In-country clinical
investigations may not be appropriate or necessary, especially if the jurisdiction has implemented good reliance practices (GRelP) (5). However, there may be situations in which a country may require a local clinical investigation – for example, where a domestically manufactured device has not previously been evaluated by a reference regulatory authority or CAB, where the domestic population has specific genetic characteristics or an ethnic composition not sufficiently represented in clinical investigations conducted elsewhere, or where a medical device intended for a particular disease or condition specific to the population requires evaluation with a specific companion diagnostic test (see section 8.6 below). In addition, a previously authorized medical device may require a new clinical investigation if the manufacturer seeks to add a previously unevaluated claim to the device’s intended purpose.

The national regulatory framework should grant to the NRA the power to regulate and oversee the conducting of clinical investigations. Manufacturers may choose to undertake a clinical investigation in a particular country, primarily to collect and provide clinical evidence to an NRA that a device for which it is seeking approval is safe and performs as intended in the population of interest. Factors to be taken into account when establishing a requirement for the clinical investigation of a medical device include risk class, technologies used, level of invasiveness, and the adequacy of existing clinical evidence and its applicability to the local population. Where there is no compelling scientifically sound justification for a new clinical investigation, ethical considerations generally do not favour such a requirement.

The regulatory framework should clearly distinguish between pre‐market clinical investigations of unauthorized devices and market-acceptability studies where a device is being tested for factors such as its ergonomics. Such market-acceptability studies are not considered clinical investigations and should not be subject to regulatory controls.

There should be a requirement that any sponsor wishing to conduct a new clinical investigation seeks prior authorization from the NRA. To ensure that adequate consideration is given to the study design and to protecting the interests of participating subjects (including through the use of informed consent), investigations should also be conducted under the oversight of a local ethics committee or institutional review board. A widely used international standard for the design and conducting of a clinical investigation

---

69 The individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation (18).


The NRA should also establish a mechanism for publishing periodic progress reports and for the reporting of serious incidents that occur during clinical investigations. The NRA should also have provisions in place to suspend or terminate a clinical investigation in the case of identified harm to patients and/or public health (68).

In-country clinical investigations (that is, systematic clinical investigation in the country in which market authorization is being sought) should not generally be a requirement. When adequate clinical evidence from another country, along with a clinical evaluation, have been provided to the NRA as part of a market authorization application, then a new in-country clinical investigation should not generally be required unless there is a compelling and sound scientific reason.

6.3.1.2 Appoint and have oversight of CABs

The performance of certain technical evaluation or auditing elements of the regulatory framework may be delegated to recognized CABs. The NRA should establish criteria for CAB recognition (see section 4.3 above). These bodies may perform initial certification and surveillance audits of device manufacturer QMS and/or pre-market reviews of the conformity of a device to the essential principles. A CAB may be recognized by the NRA to undertake conformity assessments of specific categories of medical devices where it is judged to have the necessary skills (for example, active implantable and/or IVDs and/or electromedical devices) (61, 63). Satisfactory compliance with requirements is typically documented with a CAB certificate and subject to periodic review and renewal. The NRA may consider adopting mechanisms to rely upon, or recognize, certificates issued by a CAB, even those outside its jurisdiction or direct oversight (69). Based on the CAB evaluation, the NRA then makes its final decisions on compliance and market authorization. The CAB performs its evaluation under the oversight of the NRA.

6.3.1.3 Recognition of standards

Conformity with recognized international consensus standards is a means by which the manufacturer may demonstrate that a medical device conforms to one or more of the essential principles of safety and performance consistently throughout its life-cycle.

71 Standards indicated in this document were current at the time of publication. Users should refer directly to the standards body to verify the currently used standards.
Medical device standards can largely be grouped into three categories:

- **Basic standards** (also known as horizontal standards) which cover fundamental concepts, principles and requirements applicable to a wide range of products and/or processes – these include QMS (41), risk management systems (50) and clinical investigation (18).

- **Group standards** (also known as semi-horizontal standards) which cover aspects applicable to families of similar products or processes with reference to basic standards – such as those on sterility, electrical safety or biocompatibility.

- **Product standards** (also known as vertical standards) which cover safety and performance aspects of specific products or processes – such as standards for infusion pumps, X-ray machines, blood glucose meters for self-testing and IVDs (29).

At the expanded-level regulatory controls, the NRA should establish a procedure to identify national versions of recognized international standards that it regards as providing a presumption of conformity to specific essential principles (that is, a recognized standard) (46). Preference for such recognition should be given to international standards such as those of the International Organization for Standardization (ISO), the International Electrotechnical Commission (IEC) and other international standards development organizations (SDOs). If no standards are available from international SDOs, the NRA may consider standards from regional or national SDOs. Where feasible, members of SDOs (such as ISO and IEC) should participate in standards development and in the adoption of international standards by national SDOs in a timely manner. It is also important that national standards correspond to the current versions of international standards. As international standards are periodically revised, national recognition and adoption of the updated editions will have to take place accordingly, and the NRA should establish a transition period for manufacturers to adopt and implement the new versions. To maintain the necessary flexibility in utilizing standards, it is better to adopt a system of recognizing standards through guidance documents or guidelines rather than placing the standards into legislation. These documents can then be revised and updated to stay current much faster than legislation can be.

6.3.1.4 **Select and implement a medical device nomenclature system**

An internationally recognized medical device nomenclature system (70) includes a framework for standardizing the use of internationally recognized nomenclatures for regulatory purposes. It supports collaboration between current
systems among key stakeholders to ensure convergence towards the widespread use of an international coding and classification of medical devices.\textsuperscript{72}

A nomenclature system provides for the consistent and accurate identification of medical devices with similar characteristics by a variety of stakeholders, including policy-makers, regulators, manufacturers, trade and customs officials, insurance companies, the health care sector and users. A nomenclature system is intended to improve product distribution and use, and supports timely and accurate post-market surveillance activities and medical record keeping.

For example, the identification and investigation of a potential medical device safety issue will depend on:

- correct and timely medical record keeping by the health care provider;
- exchange of information on adverse events and incidents between the health care provider and the manufacturer and/or NRA;
- comprehensive data analyses of all adverse events and incidents for a particular device type by the manufacturer and/or regulator;
- dialogue between the manufacturer and NRA regarding any performance concerns and appropriate next steps; and
- communication to health care providers of the precautions to take with a particular device type.

Several nomenclature systems exist for identifying medical devices to support regulatory decision-making, procurement and supply, and international trade and customs, as well as inventory and maintenance management. The benefits of a nomenclature system can only be realized when the same nomenclature system is used consistently and accurately by all relevant stakeholders and that nomenclature is globally harmonized. To this end, the selection of an internationally recognized nomenclature should reflect the needs of each stakeholder both individually (for example, the Ministry of Health, regulator, manufacturer, health care industry, health care providers, trade and customs officials and patients) and as a system.

The use of an internationally recognized nomenclature supports the aggregation and analysis of information – not only within a given jurisdiction but also internationally (71). An internationally recognized nomenclature system is particularly relevant for low- and middle-income countries (LMIC) who are the

recipients of medical devices from well-resourced settings (72, 73). If countries have their own nomenclature systems that are jurisdiction-specific, then device traceability in a health care system will be significantly hindered.

Fig. 6.1 and Fig. 6.2 provide suggested processes for selecting and implementing an internationally recognized nomenclature. It is important to convene a national selection committee with representation from relevant stakeholders. The selection committee would perform a landscape analysis of national nomenclature activities and select and implement an internationally recognized nomenclature system that is best suited to national requirements.

WHO recognizes three nomenclature systems most commonly used by countries:

- European Medical Device Nomenclature (EMDN)\(^{73}\)
- Global Medical Device Nomenclature (GMDN)\(^{74}\)
- Universal Medical Device Nomenclature System (UMDNS).\(^{75}\)

6.3.1.4.1 Selecting a nomenclature system

Considerations in selecting a nomenclature system include:

- Harmonization (74): the selection of a nomenclature system should consider whether the system is harmonized between various countries, regionally or internationally, to allow for pooling of data and exchange of information. Currently, several nomenclature systems are available. Selection should first be limited to those nomenclature systems that are internationally recognized, meaning that the nomenclature agency is actively contributing their terms and codes towards ongoing harmonization efforts (75) – for example, by mapping codes and terms with other nomenclature systems – and that the nomenclature contains a hierarchical structure grouped into categories.

- Accessibility and ease of use: the selection of a nomenclature system should balance the needs of all stakeholders in the health care landscape to enable consistent implementation. The required terms, codes and definitions should be publicly available and free to users.

- Governance: the selection of a nomenclature system should consider whether the system is managed in a transparent manner with a process for obtaining feedback from all stakeholders, and a quality


system for managing changes to terminology. Organizational and review structures should be in place to ensure that all stakeholders are able to provide feedback according to their needs. Processes should use a transparent methodology for the establishment and coding of nomenclature terms.

- Timely updates: the selection of a nomenclature system should consider the mechanism and periodicity of updates to medical device terms (for example, once a year). The frequency of updates should accommodate innovation in new generic types of medical devices and allow for the clear and consistent implementation of new terms by all stakeholders.

- Used in source jurisdictions: the selection of a nomenclature system should consider the systems used in jurisdictions that are the predominant sources of imported devices. If UDI regulations (see section 6.3.1.5 below) are in place or proposed, consideration should be given to the nomenclature requirements associated with UDI in the source jurisdiction.

- Language: the selection of a nomenclature system should consider the availability of versions in multiple languages, especially those used in the jurisdiction of the NRA. If an appropriate language version is not available, then the selection committee should consider the possibility of translation.

- Transferability and interoperability: the selection of a nomenclature system should take into account whether the nomenclature is compatible and can be shared and fully used in other public systems such as national device lists, procurement systems, inventory and maintenance systems, and electronic health care records. Its interoperability, traceability, configuration control, maintenance and quality assurance should be assessed. Terms and related descriptive information should be accessible through simple and intuitive search functions. A key element is that the nomenclature system should support a UDI system (see section 6.3.1.5 below).

The role of the selection committee is to select and propose to the Ministry of Health a nomenclature system to be adopted at the national level. The decision to adopt the proposed nomenclature system is vested in the Ministry who will then communicate the decision to all respective stakeholders for implementation.
Fig. 6.1
Selection of an internationally recognized nomenclature (IRN)

(1) Internationally Recognized Nomenclature (IRN):
According to Executive Board 150/14 Standardization of medical device nomenclature addendum:
EMDN: European Medical Device Nomenclature
GMDN: Global Medical Device Nomenclature
UMDNS: Universal Medical Device Nomenclature System
For more information visit the WHO nomenclature website: https://www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-technology/medical-devices/nomenclature

(2) Selection Committee to include stakeholders, i.e. members from Health Council, Ministry of Health, NRA, Health Service providers, Insurance, Med tech Industry and patients organizations.

(3) WHO Principles
According to Executive Board 150/14 - Standardization of Medical Device Nomenclature:

(4) Internationally Recognized Nomenclatures compared against WHO principles and other characteristics (as of June 2022)
6.3.1.4.2 Implementing a nomenclature

Successful implementation of a medical device nomenclature system requires significant resources, planning and coordination. Steps to consider when developing and executing an implementation plan include:

- identify which stakeholders are responsible for which aspects of implementation and how the actions of each stakeholder will affect the others. For example, a manufacturer’s ability to identify the correct term for a device impacts a health care provider’s ability to input correct information into a medical record;
- map the selected nomenclature system to existing national nomenclature systems used in the country and provide the map to stakeholders to enable adoption;
- define a transition plan to have only one nomenclature system in the country – the plan will describe which stakeholders are expected to use which aspects of the nomenclature system by what dates, and should balance the time required for each stakeholder to complete the necessary tasks against the benefits of complete implementation;
- obtain feedback from stakeholders on anticipated challenges regarding the proposed plan and adjust the plan as needed;
- execute the plan, providing clear, consistent and timely communication to all stakeholders; and
- evaluate the effectiveness of implementation, and update the implementation plan and related policies as needed.

6.3.1.5 Unique device identification (UDI) system

A UDI system provides a single, harmonized system for the positive identification of medical devices sold on the market – from manufacturing through to the distribution chain and to the patient. Health care professionals and patients would then no longer need to access multiple, inconsistent and incomplete sources in order to correctly identify a medical device and its key attributes.76

A globally harmonized and consistent approach to a UDI system is expected to increase patient safety and improve patient care by facilitating:

- traceability of medical devices throughout their life-cycle, especially for FSCA;
- identification of medical devices through their distribution and use;
- identification of medical devices associated with adverse events;
- reductions in medical errors;
- the documenting and capture of data on medical device use over time; and
- detection of SF medical devices.

UDI itself is only one component of a UDI system. The system will also include a framework requiring device manufacturers to apply UDI to the device label and to submit data elements associated with the UDI device identifier (UDI-DI) to a public UDI database (UDID). To ensure that UDI will facilitate the exchange and interoperability of device information, NRAs should adopt international best practices when creating a new jurisdiction-specific UDI system or when using an existing UDI system. UDI guidance – unique device identification (UDI) of medical devices (23) provides an internationally

---

harmonized framework for NRAs intending to develop their UDI systems, while the unique device identification system (UDI system) application guide (76) provides the necessary details and specifications.

UDI consists of two components – the UDI-DI and the UDI production identifier (UDI-PI) – and is assigned to a medical device by the manufacturer at the time of production. The UDI-DI is a unique numeric or alphanumeric code specific to a model of medical device. The UDI-PI is a numeric or alphanumeric code that identifies the unit of device production. The different types of UDI-PI include serial number, lot/batch number, SaMD version and manufacturing and/or expiry date.

The UDID is a designated repository and source of identifying information and other elements associated with a specific medical device.

A UDI system has three interrelated requirements:

1. UDI must be based on the technical specifications of government-recognized UDI-DI issuing agencies;
2. UDI must be applied to the label of a medical device and its associated packaging; and
3. UDI-DIs along with specific information about the medical device must be submitted to a UDID for the purpose of making it publicly available and to promote data sharing between regulators and other stakeholders.

Use of UDI should be one of the regulatory requirements for placing a medical device on the market. The NRA should accredit an issuing agency (such as GS1,\textsuperscript{77} HIBCC,\textsuperscript{78} ICCBBA\textsuperscript{79} or IFA\textsuperscript{80}) to operate a system for assigning UDI that complies with national and international requirements (23, 76).

One key feature of UDI systems is the requirement to assign a specific medical device nomenclature term for each UDI-DI record in a UDID. IMDRF guidance\textsuperscript{(76)} states that regulators should:

connect the device UDI-DI information with codes and terms of a nomenclature which would enable other stakeholders to: use the UDID data for activities like purchasing, stock handling, reimbursement or research; find UDID information related to similar devices or to enable regulatory authorities to effectively assess the safety and performance of product groups in the field.

\textsuperscript{77} GS1 – https://www.gs1.org/.
\textsuperscript{78} HIBCC – https://www.hibcc.org/.
\textsuperscript{79} ICCBBA – https://www.iccbba.org/.
Where the UDI identifies an individual device, the nomenclature assignments to UDI-DI records enable the grouping of products with the same or similar nomenclature assignments. Thus, the UDI system complements and helps to achieve the goal of a nomenclature system – that is, the accurate identification of medical devices with similar characteristics.

The benefits of UDI can only accrue if all stakeholders from the manufacturer to health care providers use UDI throughout their workflow systems. Therefore, it is imperative that stakeholders are educated on the development and use of a UDI system.

6.3.1.6 Control of advertising and promotion

As part of their market development efforts, manufacturers, importers and distributors generally seek to promote medical devices to health care professionals, users and/or patients. At a minimum, in all countries there should be a requirement that advertising and promotion materials should not be false, misleading or deceptive (36). The device’s intended purpose as described in promotional materials should be consistent with that for which market authorization was granted. In countries where the presence of misleading and inaccurate advertisements is a particular problem, the NRA may expand its controls to include the review of advertising and promotional materials before their publication. The NRA should also consider a role for pre-clearance agencies, which act as independent entities to review advertising materials to ensure compliance with regulatory requirements. The NRA should also consider whether existing general rules for advertising to consumers (for example, fair competition rules), including through online promotions, are sufficient for application to medical devices. If not, they should consider whether specific guidance is required. If preventive measures against false, misleading or inaccurate promotional materials are ineffective, the NRA may consider enforcement actions such as the issuance of warning letters, seizure and/or disposal of devices, fines/penalties and court orders.

6.3.2 Expanded-level regulatory controls – placing on the market

6.3.2.1 Perform in-country QMS audits

The QMS is important not only for assuring the quality, safety and performance of a device but also as the source of much of the evidence in the technical documentation used by the manufacturer to demonstrate conformity of the device with the essential principles and the associated declaration of conformity. Good record-keeping practices and record-retention policies should be observed in the QMS.

At the basic level of regulatory control, this GMRF recommends that the law should require manufacturers of all classes of medical devices to establish and
maintain a QMS. As the NRA moves to enact expanded-level regulatory controls, the requirement in law should be supplemented by a regulation or ministerial decree that gives power to the NRA to verify that a QMS appropriate to the medical devices under its control has been implemented by the manufacturer.

Although manufacturers of Class A medical devices are required to implement a QMS based on ISO 13485:2016 (41), in most countries with established NRAs, they are generally not subject to inspection by the NRA prior to market approval nor routinely inspected by the NRA after the devices have been placed on the market (see Table 4.3 above for QMS requirements for medical devices in Classes B, C and D).

6.3.2.1  QMS audit

The NRA should establish means of verifying that the manufacturer conforms to the relevant QMS requirements (41). The law should include provisions for the NRA to designate or recognize CABs (see section 6.3.1.2 above) to perform QMS audits, or to otherwise gather and assess evidence of the manufacturer’s effective implementation of the QMS requirements.

For countries in which most medical devices are imported, the option of reliance or recognition is likely to be appropriate. It will often be sufficient for the NRA to rely upon evidence (including QMS certificates) of the manufacturer’s compliance with international guidelines and recognized standards, and with legal requirements in other jurisdictions. The receiving country thereby relies upon information from the QMS audit or recognizes the decision of the other jurisdiction regarding the QMS audit. The NRA may also review and recognize the manufacturer’s own declaration of conformity and current certificates of conformity with ISO 13485:2016, issued by a recognized CAB in the case of Class B, C and D medical devices. The NRA should verify that such certificates remain valid (typically for 3–5 years) and cover the scope of medical devices and activities appropriate for the devices being imported.

In the event of suspected non-compliance or problems with the product, the NRA may perform an inspection, regardless of whether a CAB has performed a QMS audit. In cases where the NRA chooses to conduct its own inspection of the QMS of a manufacturer, importer or distributor, the inspectors should be appropriately trained and qualified (58).

6.3.2.2  Review submissions for compliance with essential principles

The NRA makes a decision on market authorization based on transparent criteria established in a law, regulation and related guidance (see also section 5.1 above). The regulation should also prescribe the form in which approval to market is given (such as a certificate or entry in a database) and make provision for post-market follow-up where appropriate (7, 20, 37).
For basic-level regulatory controls, assessing the safety and performance of medical devices depends primarily on an assessment by a reference regulatory authority supported by the manufacturer’s declaration of conformity (see section 6.2.2.2 above). At the expanded level of regulatory controls, the NRA may establish a requirement for its own pre-market review of a manufacturer’s submission or may rely on an assessment by another NRA. Guidance on the process for application and approval should be provided. This will usually be through the completion of a prescribed form or access to the authority’s web portal.

Internationally harmonized formats for the submission of technical documentation for conformity assessment purposes have been developed by various bodies – for example, the IMDRF Table of Contents (ToC) which provides a modular structure for such submissions in electronic form. Separate ToCs have been established for medical devices and IVDs (77, 78). The Association of Southeast Asian Nations (ASEAN) has also developed the Common Submission Dossier Template (CSDT) based on harmonized essential principles (79). These formats provide guidance on how to present evidence that a medical device conforms to the regulatory requirements for safety and performance.

Regulatory authorities are encouraged to adopt such harmonized and electronic formats if they require submission of technical documentation. E-submission will enhance the exchange of documentation for regulatory reliance purposes.

Sometimes there are situations that may, in the judgment of the NRA, trigger a more extensive review of the technical documentation submitted by the manufacturer. For example, when:

- the device incorporates innovative technology – that is, a new or improved product or process whose technological characteristics differ significantly from earlier devices;
- an existing compliant device is being offered for a new intended use;
- the device type is new to the manufacturer;
- the device type tends to be associated with an excessive number of incidents, including use errors;
- the device incorporates innovative and/or potentially hazardous materials;

- the device type raises specific public health concerns (particularly for IVDs);
- the medical devices classification by the relying NRA is different from the manufacturer’s assigned classification;
- the imported medical device has not been assessed and authorized by another NRA;
- the device type will be used by lay persons to support or sustain life; and
- the device is an IVD for self-testing.

The NRA should provide public guidance on the criteria for a more extensive review.

Once medical devices have been granted market authorization and placed on the market, the manufacturer may introduce changes to the product, its manufacturing process or location, or to the QMS under which it is produced. Such changes may range from minor changes (with little potential to impact the safety, performance and/or quality of the medical device) to substantial changes likely to affect the safety, performance and/or quality of the medical device. A substantial change is any change that could reasonably be expected to affect the safety or performance of a medical device or its conformity with the essential principles, and would include changes to any of the following:

- the manufacturing process, facility or equipment;
- the manufacturing quality control procedures, including the methods, tests and procedures used to control the quality and sterility of the device, or of the materials used in its manufacture;
- the design of the device, including its performance characteristics, principles of operation, and specifications of materials, energy source, software or accessories; and
- the intended use of the device, including any new or extended use, any addition or deletion of a contra-indication for the device, and any change to the period used to establish its expiry date.

The manufacturer should establish, maintain and apply a procedure for categorizing and documenting any changes to the device design/type (including software) and/or QMS as either substantial or not substantial (41, 80).

The NRA should establish guidance on changes (including a definition), and on the tools and processes used to handle such changes. The NRA should when possible, implement reliance and recognition principles when evaluating changes.
During pre-market assessment, country-specific requirements and factors should be considered, and may include local official language labelling, electrical supply, public health policies, the genetic characteristics of the population and health care delivery conditions. The NRA may also conduct a post-market conformity assessment review in response to incidents or any uncertainty concerning manufacturer compliance with the regulatory requirements.

The NRA may be assisted in reaching its decision on pre-market assessment (or any other regulatory decision) by an expert medical device committee (see section 5.8 above), which may include experts from outside the NRA. Where advice from external experts is sought, the NRA should ensure that the necessary agreements for the exchange of confidential information are in place along with signed declarations of interests. The final regulatory decision rests at all times with the NRA.

6.3.3 Expanded-level regulatory controls – post-market

6.3.3.1 Establish within the NRA processes for reviewing manufacturer post-market surveillance – including the reporting of adverse events and incidents

For basic-level regulatory controls, a system for reporting adverse events and incidents involving medical devices to the NRA – particularly those resulting in death or serious deterioration in the health of a user, patient/client or other person – is established (see section 6.2.4.1 above). At the expanded level of regulatory controls, the role of the NRA may be extended to include reviewing, as part of QMS audits, the post-market surveillance system of the manufacturer or its authorized representative, and reviewing the manufacturer’s investigation of user feedback. As a part of their QMS, manufacturers undertake post-market surveillance activities, including review of user feedback, to determine the need to report certain categories of adverse events and incidents to the NRA. The risk-management elements of the QMS require that manufacturers review the benefit–risk profile associated with the ongoing use of devices. Manufacturers may implement corrective actions to reduce the likelihood of recurrence of an event or incident. Properly structured post-market surveillance can identify serious problems in the safety, quality and/or performance of a medical device that may not have not been foreseen or detected during product development or pre-market evaluation, and can provide for corrective action. This may include the international exchange of alerts through a standardized process (26).

NRAs should ensure that manufacturers have in place a system for post-market surveillance (for example, through an ISO 13485 audit) that includes the collection of user feedback, reporting of certain adverse events and incidents to the NRA, and evaluating the need for corrective actions. The responsibilities of the NRA should encompass:
- handling of adverse event and incident reports and user feedback (including complaints) reported by the manufacturer, and setting out clear responsibilities for the manufacturer, authorized representative, importer and distributors;
- collecting and reviewing of adverse events and incidents reported by the manufacturer;
- ensuring maintenance by parties in the distribution chain (importers and distributors) of appropriate records of user feedback (including complaints) and actions taken; and
- reviewing the implementation of corrective or preventive actions, including FSCA, by the manufacturer or its authorized representative, when appropriate.

Where the manufacturer is located outside the jurisdiction of the NRA, there should be an agreement between the manufacturer and its authorized representative defining who fulfils the national regulatory requirements and maintains records of the distribution of the device. The agreement should require the authorized representative to report all incidents and adverse events and user feedback, including complaints, to the manufacturer for investigation and possible corrective action.

To the extent that investigation and information management resources allow, the NRA should establish a mandatory requirement for the timely reporting, by the authorized representative or manufacturer, of any adverse events, incidents and serious public health threats associated with the use of medical devices in the jurisdiction. It should define the threshold for reporting, reporting time limits, required information and which party (or parties) shall report. In general, such criteria should be consistent with WHO and IMDRF guidance (8–11).

6.3.3.2 Develop a system for market surveillance (see also section 6.2.4.5 above)
In addition to adverse event and incident reporting by the manufacturer, the NRA may develop a system for market surveillance. The system will include the receiving of feedback from users and patients, analyzing of data from regulatory investigations or audits, and, possibly, the targeted testing of specific medical devices on the market. The NRA assesses reports from users and may forward these reports to the manufacturer or its authorized representative for follow-up and investigation. For a systematic approach to market surveillance, the NRA may develop a risk-based plan based on data from regulatory checks on medical devices already on the market. Sampling and testing may be part of market surveillance if applied in a focused and cost-effective manner. However, the resources needed to acquire expertise and maintain testing facilities covering
the broad spectrum of medical devices are often beyond the reach of NRAs and testing laboratories. Collaborating with laboratories on a national or regional level will promote the building of expertise and improved use of resources (11).

6.3.3.3 Inspections of registered establishments

The NRA should have the power and authority to inspect, scheduled or unannounced, all registered establishments of manufacturers, importers and distributors to confirm that they have the facilities, procedures and records in place to allow them to comply with regulatory requirements. Where possible, the NRA is encouraged to rely on facility inspections or audits performed by reference regulatory authorities, CABs or other trusted institutions such as WHO. However, the NRA should retain the right to inspect all registered establishments in its jurisdiction. Inspections or audits should be based on a risk-based approach (for example, first inspect or audit higher risk-class products, facilities with recent adverse inspection or audit findings, and facilities not previously inspected or audited by the NRA). Additionally, the NRA may issue licences to registered establishments, renewable on a periodic basis. The registration – or licence if such has been issued – may be withdrawn or suspended if significant non-conformities are found during inspection and not corrected.

6.3.3.3.1 Distribution of medical devices

The manufacturer of a medical device is required to implement a QMS covering activities it performs – including design and development, production, distribution, installation, servicing and disposal. However, the quality, safety and performance of finished medical devices may be affected after release from the manufacturer to the distributor by factors such as storage conditions, warehouse environment and practices, transportation, installation, servicing, duration of storage and user training. The manufacturer then has the responsibility to:

- select and contract appropriately qualified distributors (for example, those with appropriate and adequate facilities, information systems and qualified staff);
- where appropriate, specify the requirements for medical device storage, handling, transport, installation, servicing, traceability of record keeping and disposal; and
- periodically verify the conformity of distributors with the contractual requirements.

Post-market surveillance activities, including the collection of customer feedback and implementation of corrective actions, will generally be conducted by the manufacturer through cooperation with its authorized representative and distributors.
Distributors should implement a basic QMS covering the scope of their activities. With the continuing increase in global trade in medical devices, new suppliers enter the field often without much experience or relevant qualifications. This may allow for the supply of non-conforming medical devices or, in some cases, SF medical products.\textsuperscript{82} Parties within the distribution chain should comply with good practice guidelines, such as a code of good distribution practice (GDP). Fulfilment of the requirements of GDP may be enabled by the implementation of a QMS in accordance with ISO 13485:2016. Because the scope of activities covered by ISO 13485:2016 is broader than the activities of most distributors and importers, the Asian Harmonization Working Party (AHWP, now GHWP) published guidance on the application of ISO 13485:2016 in an organization that distributes or imports medical devices (66). Widespread adoption and implementation of GDP in the medical device supply chain is an important element in preventing the spread and use of SF medical products.

6.3.3.4 Local production

Local production of quality medical devices can lead to more accessible and affordable products which will be critical for the provision of quality health services (81–83). As well as ensuring the safety, quality and performance of medical devices, governments have legitimate policy interests in promoting and encouraging the development of local development and manufacturing capacity. Local production potentially offers a cost-effective pathway to improving access to health care and medical devices. While local production is one approach to increasing access to medical devices, additional research on technology transfer will be needed to create an environment that will benefit public health. In addition, local production requires a multisectoral approach to put in place policies to ensure the manufacture of quality products. The government should ensure transparency, predictability, non-discrimination, consistency of requirements, impartiality and respect for proprietary confidential information (that is, GRP) (4). The government will play an important role in establishing the local production of medical devices including through policies, resources, mobilization of relevant government bodies and stakeholders, promoting a conducive business environment for the local production of medical devices, and the establishment of a strong NRA.

The NRA should be equipped to:

- advise the government on the preparation of appropriate policies to facilitate local production of medical devices;

\textsuperscript{82} Substandard and falsified medical products. Key facts (\url{http://www.who.int/entity/mediacentre/factsheets/fs275/en/}, accessed 8 February 2023).
- ensure adoption of relevant international standards as national standards, and to publish reference lists of standards recognized by the NRA for the purpose of demonstrating conformity with regulatory requirements;
- provide appropriate and impartial technical support to manufacturers, whether domestic or foreign. Appropriate consultation mechanisms encourage compliance with regulatory requirements by resolving misunderstandings – this may help manufacturers gain proficiency in the production of quality and safe medical devices;
- ensure public availability of concise regulations and guidelines for assessment, market authorization and post-market surveillance, equally applicable to local and foreign manufacturers;
- implement risk-based assessments and issue timely market authorizations for both locally manufactured and imported medical devices; and
- support and participate in regional initiatives for the implementation of reliance and recognition mechanisms and regulatory cooperation.

In the interests of safeguarding public health, and to ensure quality, safety and performance, local manufacturers should be subject to the same regulatory controls as manufacturers and distributors of imported medical devices. These controls should be consistent, non-discriminatory and impartial regardless of the origin of medical devices. The NRA, in the pre-market phase, should provide clear guidance on the legal requirement for both foreign and local manufacturers to submit technical documentation for the different risk classes of medical devices. Support from regulatory authorities to local manufacturers should be made available on request and should take into account the fact that manufacturers will differ due to the diversity of medical devices, different risk classes and different levels of development of manufacturer capabilities. A voluntary pre-submission meeting between the NRA and manufacturer may cover national requirements, and is an opportunity to discuss the requirements for an application and to obtain NRA feedback before an intended pre-market submission.

Where pre-market conformity assessments of higher risk-class medical devices, whether foreign or locally produced, are necessary, the NRA would generally conduct its own evaluations but may take into consideration (that is, rely upon) similar evaluations conducted by other authorities. Because a local manufacturer is physically located in the jurisdiction of the authority, the NRA would typically conduct its own QMS inspections or audits of the manufacturer’s
plant(s) and warehouse(s). Reliance and recognition mechanisms would generally not apply in such cases unless a reference regulatory authority or CAB has previously conducted such audits of the facility. Requirements for the registration of local manufacturers and distributors would be similar to those for foreign manufacturers, authorized representatives, importers and distributors, as would the requirement for listing of devices, including those for which a pre-market assessment is not required (that is, Class A medical devices).

In the post-market phase, the NRA undertakes market surveillance and imposes enforcement measures, if appropriate. The reporting system for adverse events and incidents is identical both for locally manufactured medical devices and imported medical devices. When serious public health threats occur for locally manufactured medical devices the NRA enforces corrective action by the manufacturer, whereas for imported medical devices the NRA enforces corrective action by the authorized representative and distributor.

In the case of adverse events, or incident reports or FSCA involving locally produced devices exported to other countries, the NRA may be called upon to investigate the manufacturer/exporter and/or to coordinate with foreign authorities. Local adverse event and incident reports or FSCA involving locally produced devices would be investigated and monitored by the NRA, but may still involve coordination with other relevant stakeholders.

In the case of inspections or audits to investigate suspected noncompliance or problems with products, the NRA would likely undertake the inspection. Based on the outcomes of the inspection or audit, the NRA may either allow the local manufacturer to continue its operations with corrective actions, or issue citations for non-conforming activities. Depending on the significance of the non-conformance, a warning letter, product withdrawal or even shutdown of the local manufacturing site are possible.

NRA activities such as assessing the technical dossier, performing on-site inspections and enforcing post-market requirements require specific capacity-building efforts. Development of the required expertise and competencies is vital if NRA staff are to perform these tasks effectively and responsibly (see section 9.3 below).

6.3.3.5 Regulatory testing of medical devices

In general, the routine testing of medical devices including IVDs (either imported or locally produced) by the NRA is not a cost-effective use of limited resources and is not recommended. The manufacturer has the primary responsibility for demonstrating that a device conforms to the essential principles of safety and performance, quality requirements, and all applicable national laws and regulations. Under the manufacturer’s QMS this includes any testing and documentation, all of which is subject to auditing and review by the
NRA or CAB either before market introduction or on demand. All such testing is covered by, and forms part of the basis for, the manufacturer’s declaration of conformity. As with other evidence of conformity held or submitted by the manufacturer, the testing evidence is subject to review by the NRA.

The manufacturer is also responsible for any testing that may be required as part of investigating product complaints, or adverse event and incident reports, as well for testing to verify the effectiveness of corrective and preventive actions.

As directed by the NRA, an appropriately qualified and equipped testing laboratory may undertake tasks such as:

- examination and testing of suspected SF medical devices (see section 8.5 below);
- investigation of devices allegedly involved in an adverse event;
- investigation of devices sent to the NRA by lay persons;
- systematic post-market testing of specific devices (either imported or locally produced) according to specific national public health priorities based on a plan (11);
- post-shipment lot verification of an IVD; and
- providing support for law enforcement investigations.

Given the diversity of medical devices, and the large number of medical devices in circulation, it is unlikely that an NRA will have the necessary resources to test all categories of medical devices including IVDs when testing is deemed necessary to verify their safety and performance. The work of the NRA may be supplemented through access to an independent accredited test laboratory (or laboratories). Testing of medical devices may be conducted by the national control laboratory (which is usually located within the NRA), the national reference laboratory, other external testing laboratories within or outside the country or by the medical device manufacturer in accordance with appropriate recognized international standards and guidelines.

The national regulations should include the option to outsource testing to competent laboratories. The organizational and governance structure, communications channels and responsibilities of entities conducting laboratory testing activities should be defined in the regulations. A memorandum of understanding with all stakeholders should be agreed upon and signed.

The competence of any testing laboratory should be evaluated by an accreditation body, and the NRA should further verify its competence before entering into the agreement. The national policy should also emphasize the need for provision of adequate funding for the human resources and infrastructure of testing laboratories. Countries that do not have well-resourced and accredited
testing laboratories are encouraged to adopt the mechanism of reliance on laboratory testing from other regulatory authorities or expert laboratories.

The NRA should establish criteria for the selection of testing laboratories. These criteria will include competent staff; adequate testing facilities; access to testing specimens, controls and reference materials; and analyte-specific accreditation to publicly available international standards such as ISO/IEC 17025:2017 (33) or ISO 15189:2022 (84) or equivalent. The integrity of laboratory testing should be maintained through effective implementation of an established QMS that includes policies and procedures for validation and verification of test methods and transfer of validated test methods, established standard procedures for the receipt, handling, storage and retention of samples received for quality testing and a management system for all laboratory records.

6.4 **Stepwise approach – harmonization, reliance and recognition**

Resolution WHA67.20 (1) emphasizes the importance of collaboration and harmonization and requests the Director-General of WHO:

... to prioritize support for establishing and strengthening regional and subregional networks of regulatory authorities, as appropriate, including strengthening areas of regulation of health products that are the least developed, such as regulation of medical devices including diagnostics.

and:

... to promote the greater participation of Member States in existing international and regional initiatives for collaboration and cooperation in accordance with WHO principles and guidelines.

The national regulation of medical devices takes place in an era of significant demographic changes, growing demand for access to affordable medical technologies at all levels of society in more countries, and an increasingly globalized world. These trends create a need for closer alignment of regulatory requirements and practices. Accordingly, countries that align their medical device regulations with existing harmonization guidance documents will help to advance the necessary regulatory convergence.

Resolution WHA67.20 also urges Member States to:

... engage in global, regional and subregional networks of national regulatory authorities, as appropriate, recognizing the importance of collaboration to pool regulatory capacities to promote greater access to quality, safe, efficacious and affordable medical products.
and to:

... promote international cooperation, as appropriate, for collaboration and information sharing, including through electronic platforms.

Harmonization, reliance and recognition will contribute to more effective regulatory systems, both directly and by supporting NRA capacity-building and the pooling of competence among authorities. These essential components of health system strengthening will contribute significantly towards better public health outcomes.

Table 6.3 illustrates which elements of basic-level and expanded-level regulatory controls are covered by existing international regulatory harmonization guidance (in red) and which may be implemented through reliance or recognition (in blue).

Table 6.3
Elements of regulatory controls for which international regulatory guidance has been developed and those that may be implemented through reliance or recognition
Table 6.3 continued

<table>
<thead>
<tr>
<th>Pre-market</th>
<th>Placing on the market</th>
<th>Post-market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publish law including definitions and regulations with transition period</td>
<td>Registration of establishments</td>
<td>Establish a system for reporting adverse events and incidents</td>
</tr>
<tr>
<td>Establish medical device classification for regulatory purposes</td>
<td>Listing of medical devices</td>
<td>Require mandatory notification by the manufacturer of field safety corrective actions</td>
</tr>
<tr>
<td>Establish Essential Principles of safety and performance</td>
<td>Import controls</td>
<td>Establish a procedure to cancel market authorization for products that no longer meet quality, safety or performance requirements</td>
</tr>
<tr>
<td>Establish basis for reliance and recognition</td>
<td></td>
<td>Establish a procedure to issue safety alerts to users</td>
</tr>
<tr>
<td>Establish requirements for Declaration of Conformity</td>
<td></td>
<td>Undertake market surveillance</td>
</tr>
<tr>
<td>Establish requirement for manufacturers for a Quality Management System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Establish requirements for labels and labelling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prohibit deceptive, misleading and false advertising</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Establish provisions for exceptional pre-market situations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: elements indicated in red are those for which international regulatory harmonization guidance documents have been developed. Elements that may be implemented through reliance or recognition are in blue.

7. Regulatory pathways

7.1 Regulatory pathways for pre-market conformity assessment of medical devices according to risk class

The regulatory pathways shown in Fig. 7.1 illustrate the steps required for the routine assessment of an application for market authorization for a medical device according to its risk class. Although determining the correct risk class of a medical device is primarily the responsibility of the manufacturer, a determination may be overruled by the NRA either before or after a device is placed on the market. The degree of scrutiny by the NRA or CAB of a device's conformity with regulatory requirements depends on the risk class of the medical device. Regardless of the classification and any market authorization by the NRA,
the manufacturer retains responsibility for ensuring the safety, performance and quality of the medical device, as evidenced by the declaration of conformity and supporting documents.

Fig. 7.1

**Regulatory pathway according to risk class** (see also Table 4.3 above)

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparatory stage: collecting evidence of the safety and performance of the medical device</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registration of establishment (manufacturer, authorized representative and/or importer or distributor)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparation and maintenance of the technical documentation according to requirements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence of effective implementation of QMS and declaration of conformity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISO 13485 certificate or inspection/audit from an accredited organization is required</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparatory stage: listing submission to the regulatory authority</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submission of technical documentation/dossier to the Authority/CAB (including clinical evidence and evaluation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Market authorization procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usually**, no review is required. Only notification to the regulatory authority is required.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usually, administrative review only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technical review</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-depth technical review</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approval</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRA lists the medical device</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRA issues market authorization when all requirements are fulfilled or sends notice of deficiencies or rejection.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Overseas manufacturer shall assign an authorized representative.

** Except for Class A devices that are sterile or have a measuring function: regulatory audit can be considered.
The length of the pre-market review process will vary depending on factors such as risk class of device, amount and nature of submitted evidence to be reviewed, complexity of device, degree of novelty of the device and/or its mode of action and/or its intended use, and on the availability of appropriate review staff. Fig. 7.2 shows the duration of key elements of the approval process by risk class based on best practices. The review periods shown are indicative and the NRA may consider applying different time limits. Where a jurisdiction does not require the periodic renewal of a market authorization, the indicative renewal times shown in Fig. 7.2 will not apply. Renewal intervals and review time for QMS certificates may also differ.

**Fig. 7.2**
*Duration of key elements of the approval process, by risk class*

<table>
<thead>
<tr>
<th>Device classification</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>How long you should expect to wait after submission until approval is granted</td>
<td>&lt; 1 month</td>
<td>1–3 months</td>
<td>2–6 months</td>
<td>2–6 months</td>
</tr>
<tr>
<td>Validit period for device registrations</td>
<td>3–5 years</td>
<td>3–5 years</td>
<td>3–5 years</td>
<td></td>
</tr>
<tr>
<td>Market authorization renewal should be started this far in advance</td>
<td>6 months</td>
<td>6 months</td>
<td>6 months</td>
<td></td>
</tr>
</tbody>
</table>

### 7.2 Regulatory pathways for pre-market conformity assessment of medical devices based on reliance

Reliance is a process that may apply to several regulatory activities and decisions. Examples include reliance on assessments of technical dossiers or reports of inspections or audits performed by another NRA or a CAB, and on the evaluation of incidents made by another NRA where such incidents also affect the domestic market of the NRA. Acceptance and use of the results of tests conducted by collaborating laboratories in other jurisdictions may also be considered to be reliance. Fig. 7.3 outlines the steps to market authorization for a medical device based on reliance.
Fig. 7.3
Regulatory pathways based on reliance, by risk class

<table>
<thead>
<tr>
<th>Preparatory stage: collecting evidence of the safety and performance of the medical device</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device classification is determined according to the classification rules.</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Registration of establishment (manufacturer, authorized representative and/or importer or distributor)*</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>The applicant assesses sameness** of the products, submits application and other relevant documentation based on requirements of the reference institution.</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Evidence for an effective QMS implementation and declaration of conformity</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Upon manufacturer consent, reference regulatory authority or other trusted institution exchange assessment reports with the relying NRA.</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Market authorization</td>
<td>Usually***, no review is required. Only notification to the regulatory authority is required.</td>
<td>Relying NRA conducts abbreviated assessment of the shared reports based on national requirements.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approval</td>
<td>NRA lists the medical device.</td>
<td>NRA issues market authorization when all requirements are fulfilled or sends notice of deficiencies or rejection.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Overseas manufacturer shall assign an authorized representative.

** For sameness check at a minimum name of the product, regulatory version, product code, design, labelling and packaging, intended use, IFU, manufacturing site and QMS certificate ISO 13485. Reference: Good reliance practices.

*** Except for Class A devices that are sterile or have a measuring function: regulatory audit can be considered.

Fig. 7.4 shows the duration of key elements of an approval process based on reliance, by risk class and according to best practices. The NRA may consider applying different time limits. Where a jurisdiction does not require the periodic renewal of a market authorization, the indicative renewal times shown in Fig. 7.4 will not apply. Renewal intervals and review time for QMS certificates may also differ.
Public health emergencies often stress the entire health care system. NRAs play an important role in responding to emergencies by enabling the timely availability of medical devices intended to help address the public health threat (85–93).

The NRA should establish policies and processes to allow emergency authorization of previously unmarketed medical devices, or derogation from the routine assessment procedure for previously unmarketed devices that are considered essential in managing public health emergencies. The adoption of such mechanisms enables regulatory agility in responding to an emergency and should be a critical component of national emergency preparedness.

The main purpose of an emergency regulatory authorization mechanism or derogation procedure is to allow the use of previously unmarketed medical devices during a public health emergency where the available evidence reasonably suggests a potential benefit, some minimal criteria have been met and a basic regulatory review has been performed.

Reviews should support risk-based regulatory decisions, weighing the potential risks of a previously unmarketed device against the potential risks posed by the public health emergency. Such decisions should be based on the evidence submitted to support the emergency authorization request, supplemented with additional monitoring after authorization and ongoing review of safety and performance evidence to adjust the regulatory decisions as necessary and as more evidence becomes available.

A medical device may be designated by the NRA as authorized for emergency use where:
1. The medical device is needed:
   ■ to treat or diagnose any medical condition resulting from a public health emergency;
   ■ to prevent the spread or possible outbreak of an infectious disease;
   ■ to treat or diagnose an infectious disease or any medical condition associated with an infectious disease, where the medical condition or infectious disease is potentially serious or life threatening; and
   ■ no safe and effective alternatives have previously been authorized or are reasonably available.

2. In the understanding of the NRA, there is:
   ■ preliminary scientific evidence that the medical device has the potential:
     – to treat or diagnose the medical condition resulting from the public health emergency,
     – to prevent the spread or possible outbreak of an infectious disease, and
     – to treat or diagnose an infectious disease or any medical condition associated with an infectious disease.
   ■ continued scientific evidence that the potential benefits of the medical device outweigh the known risks of the medical device to a person on whom the medical device is used, and;
   ■ a strong post-market surveillance structure and market surveillance system to monitor product safety and performance, update the benefit–risk assessment and reduce the chance of SF products reaching the market.

The applicant is required to actively seek and submit more evidence as it becomes available.

To develop and establish the minimum criteria for evaluating the safety and performance of such emergency use medical devices, the NRA should consult with experts at the national, regional or, in some cases, global level before such products are placed on the market.

Any emergency authorization strategy should provide for transparent disclosure of the evidence requirements and evaluation criteria. The NRA should also establish a limited validity period for such measures and for the

---

83 The legal person or institution that applies for registration of a product on behalf of the manufacturer (140).
authorized medical device so that the evidence assessed during the emergency period may be proved, disproved or strengthened. The period of validity of the data assessed for authorization should be clearly disclosed so that health services and professionals do not purchase or use products for which emergency authorizations have expired or been cancelled.

As part of post-market surveillance, manufacturers should continuously monitor post-market data on the safety and performance of the medical device as such evidence becomes available. When adequate supporting data have been compiled, a complete assessment of the product using routine review procedures should be conducted by the NRA.

A diagrammatic summary of these and other steps in the emergency use authorization process is shown in Fig. 7.5.

Fig. 7.5
Process for emergency use authorization
7.4 Regulatory pathway for borderline products

The field of borderline products is becoming more complex due to advances in technology, conflicting regulatory decisions and changing regulations in different jurisdictions. A lack of clarity in such cases may lead to difficulty in determining appropriate regulatory requirements. In some jurisdictions, no separate regulation or specific guidance for such medical products exist. It is in the public interest to ensure the safety, quality and performance of all borderline products through appropriate regulatory controls, either those used for medical devices or those used in other regulated products sectors.

7.4.1 Background information and approaches to improve the regulation of borderline products

Although many products are used in the delivery of health care, not all fit exclusively within the existing definition of a single category of medical product, and more specifically that of a medical device. An increasing number of products are characterized as borderline – an ambiguity that exists for either innovative products that do not clearly fall under current regulations or those that fall within the overlaps of existing regulations. For reasons of transparency, predictability and proportionate regulatory control, it is important to have established demarcation lines between different product categories. This will allow for the identification of appropriate regulatory requirements and authorization pathways under legislation most appropriate for such products (94–100).

Borderline products are considered to be products where it is not immediately clear whether a given product is to be regulated as a medical device or as something else (Fig. 7.6). In the absence of internationally harmonized guidance, these products often pose a challenge to medical device regulators across the world.

Some medical devices have characteristics that place them near the definitional borderlines with medicines, cosmetic products and implants, air purifiers, PPE, biocidals, blood products, herbal products, information and communication technology products, assistive devices and medical gases, as well as products for general laboratory use, products used for hospital support or infrastructure, products for personal or home use, and products for common use employed as parts or accessories of health care products.

---

84 Borderline products are generally (medical) products that have characteristics covered by at least two bodies of legislation (for example, both medical device and medicine), where the primary or lead legislation within a jurisdiction may be unclear. In the context of use in combination with other medical products or components, some products that appear to be borderline may instead be considered to be combination products (see also section 7.5 below).

85 This is not intended to be an exhaustive list of borderline products but rather to provide illustrative examples.
A product may be considered to be a medical device in some countries but not necessarily in others. Manufacturers should always refer to the definitions of a medical device and other relevant regulations in the country in which an application is planned (101–103).

To ensure predictability and transparency, the NRA should develop criteria and mechanisms for determining the appropriate regulatory regime for borderline products through established guidance. It should describe the considerations and process whereby an applicant may obtain an advisory opinion from the NRA. Where necessary, that process should allow for consultation with subject matter experts as well as with regulatory authorities from other product sectors and with the manufacturer(s) concerned. It may also take into account regulatory decisions made by the regulatory authorities of other jurisdictions. After appropriate review and consultation, a product may be deemed to be subject to regulation as a medical device even though it may not clearly fall within the statutory definition of a medical device. Such a designation may be based on interpretation of the NRA’s rules and regulations for medical product
classification, technology, primary mode of action, medical claims made by the manufacturer, and intended use and indications for use of the product (for example, cosmetic contact lenses, wound-healing gel, etc.).

NRAs may take decisions on a case-by-case basis, considering all the characteristics of the product and its medical purpose. A committee or working group on borderline products may be appointed to advise the NRA when deciding on the designation of a product. The decision of the NRA on the regulatory status of a given product should be published and the option of appeal provided should the applicant disagree with the decision.

7.4.2 **Points to consider in determining whether a product is a medical device**

NRAs should refer to the medical device definition when making any borderline product determinations (6). It is important to note that not all equipment used in health care settings or by a health care professional meets the definition of a medical device.

In order to decide whether a product is a medical device, the NRA should consider:

- how the product is presented to the NRA and to the market in terms of labelling, packaging, promotional literature and advertisements, including on websites;
- the intended purpose of the product, as declared by the manufacturer, including the claims made (both explicit and implicit);
- the claimed “medical purpose” as outlined in the definition of a medical device given in section 4.1 of this GMRF;
- the mode of action – medical devices do not attain their primary mode of action through pharmacological, immunological or metabolic means, but may be assisted by such means; and
- whether there are any similar products on the local market and how they are being regulated.

Some of this information may be obtained by consulting with regulatory authorities for other product categories. If available, the applicant may submit evidence of product classification and market authorization by a reference regulatory authority. A proposed process for making a borderline product determination is shown in Fig. 7.7.
Fig. 7.7
Process for borderline product determination

Inquiry issued by applicant to determine if the product is a medical device or not

Ask for ToC, labels, IFU, QMS. Consulting database of other NRA’s, literature, experts, stakeholders

Check if it meets the medical device definition

Is it intended by the manufacturer to be used for a medical purpose?*

YES

Non medical devices (cosmetics, ICT products etc.)

NO

Is the mode of action pharmacological, immunological or metabolic?

YES

Medical device

NO

Are there sufficient data to claim?

YES

Request for additional documentary evidence to applicant

NO

Committee or working group on borderline products

Decision on product status

Inform / meet with applicant

Publish decision

* At this point it is important to check all the medical purposes described in the medical device definition and verify if the product under analysis meets one or more than one of these medical purposes.
7.5 Regulatory pathway for combination products

There is no internationally harmonized definition of a combination product.\textsuperscript{86} If defined, the definition may vary across regulatory jurisdictions, especially as the field continues to evolve. A combination product is typically defined\textsuperscript{87} as a product consisting of two or more different types of medical products (that is, a combination of a medicine, device and/or biological product). The medicines, devices and biological products included in combination products are referred to as the constituent parts of the combination product. The medicine constituent of a combination product may be a pharmaceutical, radiopharmaceutical, natural health product, biological, cell, tissue, organ, gene therapy or human blood and its components.

Some jurisdictions have distinct definitions for medicines and biologicals. As a result, there may be both medicine-device and biological-device combination products.

The evolution of medicines and medical technologies worldwide has created a broad spectrum of medicine-device combination products that range from long-established and relatively simple in nature to highly complex. Examples of medicine-device combination products include drug-eluting stents, pre-filled syringes, transdermal medicine patches, metered dose inhalers, heparin-coated vascular catheters and orthopaedic bone cement containing antibiotics.

Combination products constitute a distinct category of medical product subject to specific regulatory requirements. The requirements for combination products arise from and combine elements of the separate statutory and regulatory requirements applicable to medicines, devices and biological products. These requirements may need to be adapted when applied to the constituent parts of a combination product, either alone or in combination. Specific regulatory requirements for combination products are generally designed to address the risk-based considerations raised by the combined use of the constituent parts. These may include the overlaps and distinctions between the requirements applicable to the drug, device and biological product constituent parts that constitute them, and specific requirements for their use in combination (\textsuperscript{104, 105}).

\textsuperscript{86} A combination product is defined by many jurisdictions as a product comprising two or more different types of medical products (that is, a combination of a medicine, device and/or biological product with one another) such that the distinctive nature of the drug component and device component is integrated in a singular product.

7.5.1 **Considerations in regulating combination products**

In the interests of consistency, transparency and predictability, the NRA should publish the guidance it has adopted on how to:

- determine what qualifies as a combination product;
- designate an appropriate regulatory pathway; and
- establish suitable pre- and post-authorization requirements.\(^{88}\)

The NRA should publish designation criteria and establish a process by which an applicant may obtain a designation decision from the NRA. Where necessary, the process may allow for consultation with subject matter experts as well as with regulators from other product sectors, and with the manufacturer or authorized representative concerned. Regulators may also take into account determinations made by the NRAs of other jurisdictions. The NRA may take decisions on a case-by-case basis, taking into account all of the characteristics of the product. The decision of the NRA on the designation of a given product should offer the option of appeal should the applicant disagree with the decision.

The NRA should designate a product that combines a medicine, a biological product and/or a device as a combination product. Some combination products will be designated as primarily subject to the regulatory requirements for medicines and others to the requirements for medical devices. The designation may be based on the primary mode of action (40) by which the product achieves its intended therapeutic or diagnostic purpose. Where this is achieved by pharmacological, immunological or metabolic means, the combination product should be primarily subject to medicine regulatory requirements. Where the principal action is not achieved by pharmacological, immunological or metabolic means, but may be assisted in that action by such means, the combination product should be primarily subject to medical device regulatory requirements.\(^{89}\) Elements of both medicine and medical device regulations may be applicable (106, 107).

Product designation should lead to the development of a single product-specific pathway for market authorization, combining elements of both sets of requirements. Creating such a single regulatory pathway will help streamline effective product review, while taking into account the particulars

---

\(^{88}\) Good manufacturing practice/QMS requirements may be developed specifically for combination products (for example, [https://www.fda.gov/media/90425/download](https://www.fda.gov/media/90425/download), accessed 9 February 2023) or should follow the regulatory requirements of the constituent parts of the combination product.

\(^{89}\) If a medicine is incorporated in a medical device, according to the IMDRF classification rules, it is always a Class D medical device ([https://www.imdrf.org/sites/default/files/docs/ghtf/final/sq1/technical-docs/ghtf-sq1-n15-2006-guidance-classification-060627.pdf](https://www.imdrf.org/sites/default/files/docs/ghtf/final/sq1/technical-docs/ghtf-sq1-n15-2006-guidance-classification-060627.pdf), accessed April 2022).
of each constituent part. It will also reduce any overlapping administrative requirements. The pathway will determine both the type of application, data requirements and type of market authorization review process required for the combination product, with the criteria for review differing depending on whether the product is designated as predominantly a medicine or as a medical device.

In addition to directing the combination product into the appropriate regulatory pathway, the NRA should also decide on the extent of the requirements to apply to its constituent parts. For example, the safety and performance of the medical device that contains a medicinal substance should be verified as a whole, along with the identity, safety, quality and efficacy of the medicinal substance in its intended function in the specific combination product \(108\). The pathway should provide for timely and appropriate consultations and information exchange between medical device and medicines technical experts during the process of reviewing the market authorization application.

Beyond the pre-market evaluation requirements, the NRA should establish specific requirements for the manufacturing, quality assurance, testing and distribution of the combination product. These requirements would generally be based on established medicines good manufacturing practices (GMP) or medical device QMS requirements, adapted as appropriate to the product designation. The NRA should also establish requirements for inspections and audits, either by the NRA or CAB. Depending on product designation, the NRA should also establish specific requirements for post-market surveillance and adverse event and incident reporting, adapted as appropriate from the respective medicines and medical device requirements. As both the medicines and medical device NRA departments will have an interest in adverse events and post-market surveillance field performance information, an effective coordination mechanism should be implemented.

The use of reliance and recognition in evaluations of medicine-device combination products may be more difficult due to the diversity and complexity of such products and to differences in regulations between jurisdictions. General reliance principles (see section 5.9 above) should be applied. As there is currently no international harmonization guidance for combination products, NRAs using reliance or recognition should consider which requirements in other benchmark jurisdictions would best serve their country’s needs. Given the current challenges in the regulation of combination products, medical devices stakeholders should support and encourage international regulatory harmonization forums in pursuing convergence and harmonization efforts in this field.
7.6 Regulatory pathway for donated medical devices

Donations to LMIC of medical devices including IVDs can be very helpful and may improve the efficiency of health facilities, save on the costs of purchasing new medical devices, and make some diagnoses or therapies accessible to patients, especially in resource-limited settings. Although donations may thus be beneficial, they can also pose health risks if the safety and performance of the donated medical devices are not verified and/or the devices do not correspond to the clinical needs, use environment and skills of end-users and local technical staff. Other potential challenges include the lack of clear documentation, appropriate labels and labelling on the donated medical device, and data on its state, origin and technical and service history. There is also often a lack of clarity regarding the responsibilities of donors (109).

Quality and other problems associated with donated medical devices have been reported in many countries (110, 111). Such problems have included short or outdated expiry dates, defective medical devices90 and gifts or donation of unnecessary items not requested by the recipient. These factors often result in the receiving countries incurring unwanted costs for the maintenance and disposal of the donated medical devices. Donations may also create the impression that the medical devices are “substandard” or even waste that donors have “dumped”91 on receiving countries (110–112). For these reasons, some countries have banned the donation of used equipment. Before donating medical devices including IVDs, WHO recommends (112) that a number of core principles be taken into account, including that donated devices should:

- address an expressed request from the end-users, corresponding to a real clinical need;
- be authorized by the regulatory authorities of the receiving country and/or meet current international safety standards;
- have all their necessary parts and accessories;
- be accompanied by documentation in a language understood in the receiving setting;
- be adapted to the local context, such as the electrical power supply;
- match the operating and maintenance human resources, skills and capacities and/or be accompanied by training; and

---

90 Donated used durable medical equipment is often not accompanied by documentation of its calibration, service and maintenance or refurbishment history. Whereas a device may have conformed to relevant safety, quality and performance standards at the time it left the original factory, its continued conformity may no longer be assured or presumed.

91 The dumping of obsolete equipment by high-income countries has been described as “morally reprehensible” (111).
be imported with a plan for their disposal in the receiving country after prior investigation and (if possible) identification of a disposal solution to be implemented once the medical device has reached end-of-life and can no longer be used.92

Authorities in countries from which donations originate are urged to develop policies, regulations and guidelines on the exportation of donated medical devices to other countries, particularly to prevent the export of waste or hazardous medical devices to LMIC. A national policy for donations in the receiving country is also vital for guiding all parties involved so that they may develop their own institution-level operational donation guidelines and standard operating procedures based on this policy.

Policy on donations should cover the following three phases:

1. Pre-donation phase – assessment and identification of potential recipient(s), familiarization with requirements, donation proposals, agreement between donor and recipient, application to obtain authorization to export/import donated medical devices, commitment letter confirming their safety and performance, and application to import/export.

2. Donation phase – importation, document verification, physical inspection, sample collection (where applicable) and verification studies (where applicable).

3. Post-donation phase – installation and commissioning, verification of functioning status and post-market surveillance;93 this implies feedback to the donor on device performance and post-market surveillance data.

To safeguard public health, medical devices imported as donations should comply with all regulatory requirements on safety, quality and performance, and should not differ in this regard from devices imported through a regular supply chain. It is the responsibility of the donor, charity organization, private person or medical devices company – in consultation with the recipient and vice versa – to ensure that medical devices intended for donation are in compliance with the

---

92 Upon arrival, the remaining shelf-life of the medical devices (specifically IVDs) should be reasonable and should allow for the use of the entire donated lot according to the specifications set between donor and recipient (https://apps.who.int/iris/bitstream/handle/10665/255577/9789241512558-eng.pdf, accessed 15 January 2023).

93 Donated devices may (probably will) be beyond their manufacturer warranty period. Importers should be informed of, and take into consideration, that fact and the possible expenses associated with preventive and corrective maintenance and lack of spare parts.
Annex 3

regulatory requirements of the receiving country. This also applies to donations made within a jurisdiction. Even during emergency situations (such as natural disasters, pandemics, etc.) public safety takes precedence and recipients should therefore still take action according to the national guidance on donations.

Regulatory authorities should establish a mechanism to verify and authorize the importation of donated medical devices. Institutions that intend to donate devices should communicate with the recipient to determine their needs, make relevant donation proposals and obtain their approval before the products are shipped. To avoid delay and additional expense, importation documents and supporting documents must be submitted to the NRA of the recipient’s country for assessment and authorization before shipment of the consignment. These documents will typically include but are not limited to: (a) a list of the products to be donated; (b) each product’s (package) label; (c) name and address of the manufacturer(s) of the products; (d) evidence that the products are approved/authorized in the donor’s country or the manufacturer’s QMS certificate (for high risk class medical devices); (e) expiry dates (if applicable); and (f) a commitment letter confirming the safety and performance of the devices to be donated, along with all documentation of proof of proper functioning (112). All donors are required to familiarize themselves with the donation requirements in force in the receiving country before they decide to donate medical devices. Donations that do not comply with the requirements should be rejected and sent back to the donor at the donor’s expense. The typical steps and stakeholder responsibilities in the donation of medical devices are shown in Fig. 7.8.

8. Additional topics

Beyond the general elements covered in earlier sections of this GMRF there are also a number of specific topics that must be considered when developing and implementing regulations for medical devices. This section explains the relevance of these topics and provides guidance for regulators on ensuring that they are appropriately addressed.

8.1 Disposal

A medical device that reaches the end of its intended life-cycle must be disposed of safely according to the manufacturer’s recommendations and local regulations. In some cases, it may be necessary to dispose of and destroy a device before the end of its life and to ensure that it will not be re-used if it is confirmed that the device can no longer perform its function properly and may present a hazard to users or patients.
The disposal of a medical device should follow safety procedures to ensure that it does not cause harm to people or the environment. This is especially important for contaminated devices such as syringes or hypodermic needles, and devices that contain infectious agents, hazardous waste, toxic or radiological materials, electronic components or potentially pathological materials such as human organs or unused blood products. Medical device labelling and the IFU or e-labelling should include instructions on the proper decontamination and disposal a device at the end of its life-cycle. Where the NRA has identified SF
medical products, it shall itself document a procedure for their local disposal (for example, mandatory destruction at an approved facility). This will ensure that such SF products are not exported to another country where they may cause harm.

Owing to their diversity and complexity, there are many ways that medical devices may be disposed of. For durable equipment, mechanisms may include replacement and decommissioning. For disposable devices or IVDs, decontamination and proper waste management practices according to the manufacturer’s instructions should be followed based on national and international standards. The responsible NRA, in coordination with other concerned governmental bodies, should establish criteria for replacement and decommissioning based on the manufacturer’s recommendations. Consultation between the user and manufacturer is critical, especially for high-technology and complicated products, in order to decide upon the best way to dispose of them. Separate guidance is to be provided to the health care system by the Ministry of Health on the disposal of hospital waste.

8.2 Reprocessing of single-use medical devices

In general, regulatory and public health concerns about the reprocessing and re-use of devices labelled by their original manufacturer as single-use medical devices (SUMDs) include: lack of regulatory controls and oversight, responsibilities for reprocessing not established, variability in reprocessing methods, risk assessment not performed, and reprocessing not performed under a QMS, which all lead to lack of control with regard to cross-infection, contamination, residues of disinfectants, mechanical failure, endotoxins and labelling.

The perceived advantages to health care practices of cost–effectiveness and waste reduction measures must be weighed against the potential risks associated with reprocessed SUMDs. These risks include possible cross-infection as a result of the inability to assure the complete removal of viable microorganisms, inadequate cleaning, decontamination and removal of pyrogens, and material alteration. Exposure to chemical cleaning agents may cause corrosion or changes in the materials of the device that could pose a risk to patients. Exposure to repeated sterilization processes may also change the properties of, or degrade, the device material. The high temperatures and harsh chemicals sometimes

94 An example of specific guidance on the disposal of unfit products can be found at: https://trade.tanzania.go.tz/media/THE%20TANZANIA%20FOOD,%20DRUGS%20AND%20COSMETICS(%20medical%20device)%20regulation.pdf, accessed 10 February 2023.
96 Single-use medical devices (SUMDs) are also referred to as disposable devices or single-use devices (SUDs).
used during reprocessing may also impair the safety, quality or performance of reprocessed devices.

In addition to the potential health risks associated with the use of reprocessed SUMDs, ethical considerations also arise. They include potentially exposing a patient, with or without informed consent, to harms to which they would not otherwise have been exposed, and whether it is justifiable to treat a patient with a reprocessed SUMD that may be of lower quality, performance or cleanliness than it had when used for the first time. For regulatory and liability purposes, the entity that reprocesses a medical device becomes the new manufacturer with all the associated responsibilities. If fully accounted for, the costs of reprocessing an SUMD using a controlled and validated process are such that the claimed savings may not be realized.

A device designated by the original manufacturer and labelled as single-use should not be re-used, except in extremely rare and dire situations, and then only as subject to specified controls (see next paragraph below). SUMDs are not intended to be reprocessed and used again, even for the same patient. They should only be used in or on an individual patient during a single procedure and then discarded. SUMDs are not provided with appropriate instructions for cleaning, disinfecting or sterilizing after use, and the manufacturer generally has not investigated deterioration in safety and device performance if subject to reprocessing. Because device conformity to its original specifications for safety, quality and performance cannot be assured, a patient or user may be endangered when SUMDs are reprocessed and used more than once.

In exceptional situations, the NRA, after considering all potential risks and benefits, may opt to allow the reprocessing of specified SUMDs (43, 113, 114). In extremely rare and dire situations, such as a global pandemic, reprocessing may be permitted even if the devices do not fully meet the specifications of the original manufacturer (115, 116). The conditions applicable to these situations are restricted to specific medical devices, for example single-use surgical masks and respirators, for a limited period of time and only after performing a validation of the reprocessing process. In such circumstances, the NRA should develop specific guidance that describes the conditions applicable to the reprocessing and labelling of SUMDs, whether by a third-party manufacturer or a health care facility.

In adopting a policy on the reprocessing of SUMDs in non-emergency situations, the NRA should require that the reprocessed SUMD meets the same initial standards as those of the original manufacturer. The entity placing reprocessed SUMDs on the market is considered to be the manufacturer

for regulatory purposes (43, 113, 117) and assumes all the obligations of a manufacturer, including assuring safety, quality and performance, labelling, the declaration of conformity, post-market surveillance and incident reporting. That entity also takes on the obligations to: (a) conduct a risk assessment (including analysis of device construction and materials, and use of procedures to detect changes in the design of the original device, as well as in its planned application after reprocessing); (b) validate the reprocessing process; (c) establish a QMS; and (d) ensure traceability after product release (117, 118). The original manufacturer should be identified in the technical dossier submitted to the NRA. The label of the reprocessed SUMD does not necessarily carry the name of the original manufacturer – however it should carry the name of the entity reprocessing the SUMD and should clearly indicate that the SUMD has been reprocessed (119).

8.2.1 Reprocessing SUMDs – health care facilities
Regulatory requirements for reprocessing should also apply to a health care facility reprocessing SUMDs for re-use within its own facility. The reprocessing of an SUMD in a health care institution must be performed so as to ensure the safety, quality and performance of the reprocessed medical device. This would include: (a) conducting a risk assessment (including analysis of device construction and materials, and use of procedures to detect changes in the design of the original device); (b) validating procedures for the entire process, including cleaning steps, product release and performance testing; (c) establishing a QMS; (d) reporting incidents involving reprocessed devices: and (e) ensuring the traceability of reprocessed devices (36). If a health care facility is not able to meet these conditions, it shall refrain from reprocessing SUMDs (120, 121).

If a hospital performs SUMD reprocessing for sale or transfer to another entity, then it must conform to the regulatory requirements applied to commercial third-party reprocessors.

8.2.2 Post-market surveillance of SUMDs
Post-market surveillance requirements apply to all medical devices, including reprocessed SUMDs regardless of the entity that reprocessed the SUMD – whether this is the original manufacturer, commercial reprocessor or health care facility. When investigating incidents and adverse events, the NRA should consider the possibility that the reprocessing of SUMDs may have been a contributing factor.

8.3 Refurbishing medical devices
Some durable electromedical devices or mechanical medical devices are meant to be re-used many times over a long design life. To assure their continued safety and performance, preventive maintenance, service, calibration and repairs are
often required once a device is placed into service. In some cases, devices may also be subject to refurbishing by an organization or entity other than the original manufacturer to extend their service life, often for economic reasons, either for the original purchaser or for sale to another party.

Refurbishing may be described as the restoration of a device to a condition of safety and performance that is comparable to its condition when new (42, 122–124). This includes reconditioning, installation of software and/or hardware updates that do not change the intended use of the original device, and replacements of worn parts or parts with known limited service lives. Refurbished medical devices should be identified as such on the labelling and in commercial documents. Spare parts supplied for the replacement of existing components of a medical device that has already been put into service are not usually considered to be medical devices. If, however, those parts are likely to significantly change the intended purpose, characteristics or performance of the finished device then their installation may be considered as a change to the medical device and should be assessed accordingly.

In adopting a policy on refurbishing, the NRA should clearly state that the entity responsible for refurbishing and the refurbished device itself must meet the same regulatory requirements as applied to the original medical device. A party that refurbishes medical devices will be subject to the same requirements of safety, quality and performance, including the QMS certificate, technical documentation and declaration of conformity, as manufacturers of new devices. Insofar as they may affect the safety, quality, performance and/or conformity of the finished device, the NRA should also clearly state the role of the original equipment manufacturer in providing information to facilitate device maintenance, service and repair, as well as decommissioning at the end of service life (125). For regulatory purposes, the routine maintenance and repair of a device and replacement of parts should not be considered refurbishment.

8.4 **New medical device technologies – software as a medical device (SaMD) and software in a medical device (SiMD)**

Medical devices and health care are increasingly incorporating emerging technologies, including computing platforms, connectivity, software and sensors in diverse and interoperable systems. These technologies hold the promise of improved safety, performance and reliability, smaller size, energy efficiency, remote use by less-skilled operators, and new therapeutic and diagnostic capabilities. Current examples of such technologies include standalone software for medical purposes, networked systems, computational modelling and simulation, machine learning (ML) and artificial intelligence (AI). A decision to regulate SaMD depends on whether it meets the requirements of the statutory definition of a medical device.
The IMDRF defines medical purpose software as generally including:

- software as a medical device (SaMD); and
- software in a medical device (SiMD) – sometimes referred to as “embedded” or “part of”.

SaMD may have requirements and limitations defined by the platforms on which it is intended to be deployed, and on the broader connected systems in which it may be used. SiMD may have similar considerations to SaMD but may also have functional requirements that are driven by the relationship between the software and hardware components of the device (45).

AI is a branch of computer science, statistics and engineering that uses algorithms or models to perform tasks and exhibit behaviours such as learning, making decisions and making predictions (126). ML is a subset of AI that allows systems to “learn” through data analysis without models being explicitly programmed. An ML-enabled medical device (MLMD) is a medical device that uses ML, in part or in whole, to achieve its intended medical purpose. For “traditional” medical devices, manufacturers generally make modifications by planning future changes and collecting data before performing a planned change request and, in some cases, obtaining a new market authorization. One potential of MLMDs is the ability to incorporate continuous learning, where the MLMD may be continuously exposed to new data such that its performance may change as it learns and adapts continuously over time, rather than being updated through discreet manufacturer-initiated modifications. While continuous learning has potential benefits in maintaining or improving the performance of MLMDs in real world use, such learning also presents unique risks and may require different approaches to oversight than other software or hardware medical devices (35, 127).

Because of their many possible implementations, when establishing a regulatory approach for SaMD it is important to clearly define the scope and characteristics that:

- meet the definition of a medical device;
- should be the focus of regulatory oversight; and
- require specialized approaches to their review and oversight that may differ from hardware medical devices (128).

While medical device software may provide significant potential benefits in improving patient access and quality of health care, these technologies may also present different regulatory challenges than those associated with hardware medical devices. For example:
Medical device software might behave differently when deployed in different hardware platforms.

Often an update made available by the manufacturer is left to the user of the medical device software to install. Device software functions are often modified or updated more frequently than hardware medical devices or hardware components. The option to provide or push updates remotely may lead manufacturers to place more responsibility on device users themselves to perform updates than may generally be the case with hardware devices.

Due to its non-physical nature (a key differentiating characteristic), medical device software may be duplicated in numerous copies and widely spread, often outside the control of the manufacturer (62, 127, 129).

A plan for clear and timely communication between manufacturers and device users over the life-cycle of the software may be a critical consideration when evaluating the safety and effectiveness of device software functions in the context of their use.

In addition to the general considerations of medical device safety, quality and performance, device software functions must also be secure to ensure their continued safe functionality. The need for effective cybersecurity has become more important with the increasing use of wireless, internet and network-connected devices. Several cybersecurity incidents have rendered medical devices and hospital networks inoperable, disrupting the delivery of patient care across health care facilities (130).

Regulatory systems must have the capacity, either directly or through reliance, to accommodate the diversity of both SaMD and SiMD, and to assure high levels of device safety, quality and performance. Consistent with GRP, regulatory controls should be proportionate to the risks and benefits, including those arising from the technologies incorporated in devices.

Using a risk-based approach based on the intended use of SaMD, IMDRF has published a proposed risk-categorization framework (51). The framework proposes that the intended use of SaMD can generally be described using two factors – “A: Significance of the information provided by the SaMD to the health care decision, and B: State of the health care situation or condition.” Based on these two axes, the framework proposes that SaMD can then be categorized into four categories (I–IV), with category IV devices considered to be of very high impact (51, 131).
Table 8.1  
SaMD categories98

<table>
<thead>
<tr>
<th>State of health care situation or condition</th>
<th>Significance of information provided by SaMD to the health care decision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treat or diagnose</td>
</tr>
<tr>
<td>Critical</td>
<td>IV</td>
</tr>
<tr>
<td>Serious</td>
<td>III</td>
</tr>
<tr>
<td>Non-serious</td>
<td>II</td>
</tr>
</tbody>
</table>

While applicable to device software functions broadly, the IMDRF notes that:

... a SaMD manufacturer is expected to implement on-going lifecycle processes to thoroughly evaluate the product’s performance in its intended market (13).

It is important that, for both SaMD and SiMD, manufacturers demonstrate:

- scientific validity – refers to the extent to which the SaMD’s output (concept, conclusion, measurements) is clinically accepted or well founded (existence of an established scientific framework or body of evidence) and corresponds accurately to the real world health care situation or condition identified in the SaMD definition statement;
- analytical validity – measures the ability of SaMD to accurately and reliably generate the intended technical output from the input data; and
- clinical performance – the ability of a device to yield results that are correlated with a particular clinical condition/physiological state in accordance with the target population and intended users (13).

The manufacturing of SaMD, which is a software-only product, is primarily based on development life-cycle activities and is often supported by automated software development tools. However, the principles in a QMS will continue to provide structure and support to the life-cycle processes, and QMS

---

98 From Table 8.1 source document (51): The approach developed in this document is intended only to establish a common understanding for SaMD and can be used as reference. This document is not intended to replace or modify existing regulatory classification schemes or requirements.
activities will still be applicable and important in controlling the quality of SaMD (132, 133). NRAs and CABs should consider what relevant expertise is required for reviewers and QMS auditors of SaMD, and whether that expertise can best be acquired directly or through reliance on the work of reference regulatory authorities.

Increasingly, medical devices that employ SaMD and SiMD, including MLMD, are being made available in regions with limited regulatory systems and capacities, and that are primarily dependent on imported products. The NRA or CAB should verify that the data used in development, verification and ML databases are representative of the local population and conditions. Data quality assurance and data management should be taken into consideration as part of the manufacturer’s QMS and requirements for evaluating dataset quality should be established. Training datasets and test datasets should be maintained independently of each other. Monitoring of the MLMD post-deployment will help to ensure its continued safety and performance, as potential variations in real-world data may impact upon the robustness and generalizability of algorithms (132).

Policy-makers and NRAs in jurisdictions with limited regulatory systems should consider:

- Regulatory priority setting – a detailed in-country pre-market assessment of the summary technical dossier for a medical device that is already authorized for placing on the market in countries or regions with mature regulatory systems may not be the most appropriate use of limited local resources. The NRA in countries with less developed regulatory systems should consider whether reliance could be used to provide evidence during the assessment of SaMD and SiMD, including evidence of the safety, performance and quality of MLMDs. Local review should focus on, for example, the local burden of disease and the applicability of the device to local population(s). It should also consider the need for regular software updates, the adequacy and appropriateness of labelling and promotional materials in the local language, local distribution practices, appropriateness for local conditions of use and maintenance, user training, and local post-market surveillance requirements. Because SaMD can be placed on the market quickly, widely and in large numbers, appropriate requirements for post-market surveillance, clinical evaluation and risk management must be in place (13, 51, 132, 134). Beyond the general requirements for post-market surveillance, and adverse event and incident reporting, regulators should also consider establishing specialized protocols for the market surveillance of SaMD, SiMD and MLMDs that incorporate the collection of real-world evidence (11).
Recognized international standards – as part of the pre-market conformity assessment process, the NRA should verify the extent to which the manufacturer and/or applicant have applied recognized international standards in device design, development, verification and manufacture. This is especially important in the case of software (either as a standalone device or incorporated into a device) and networked device systems as they generally cannot be verified by inspection or testing alone.

Appropriateness to local populations and conditions – for MLMDs the NRA should consider whether the clinical study participants and datasets adequately reflect the intended patient populations (for example, with regard to age, sex, race and ethnicity, disease severity and co-morbidities), disease prevalence and local standards of medical practice. If it is expected that a device’s performance will change over time as it “learns”, then the NRA should examine how its continued safety, risks and benefits will be assured under local conditions. The expertise of data and computer scientists, as well as biomedical engineers or other professionals with appropriate engineering and clinical expertise, may be required to perform the assessment of risks.

Health care professional intervention – in some cases, MLMDs are intended to supplement or take the place of a health care professional. The NRA should evaluate whether the MLMD has been designed for human interaction and oversight appropriate to its intended use in the local context.

Data handling and network safety – the NRA should assess the extent to which user or patient data is generated and processed in the device itself or is imported from, exported to or processed in locations outside the NRA’s jurisdiction. The regulatory risk assessment should include evaluation of safety in the event of network failure or degradation. This may require coordination with the national telecommunications, privacy and cybersecurity authorities.

Advances in state-of-the-art technology – as much of the technical expertise in these device fields may lie outside its jurisdiction, the NRA should consider how to develop relevant regulatory knowledge and experience, either at national or regional level, perhaps through consultation with local academic institutions. The NRA should also follow the development of new international standards (for example, IEC, ISO, ITU and IEEE”99) and/or evolving harmonized regulatory

---

guidance – for example from IMDRF, EU, USFDA, Therapeutic Goods Administration (Australia), Health Canada, and the Ministry of Health, Labour and Welfare (Japan).

8.5 **Substandard and falsified medical devices**

Substandard and falsified (SF) medical devices are harmful to the health of patients, damage confidence in medical products and health care providers, and increase the burden on health systems.

SF medical devices can result from genuine manufacturing errors or deliberate falsification of a product. The latter is usually a clandestine activity, often difficult to detect and designed to deceive a health care provider or patient into falsely believing that the device is the genuine article and has been carefully assessed in terms of safety, quality and performance.

Reports of SF medical devices have emerged from all over the world. WHO publishes and regularly updates its list of Medical Product Alerts, which includes SF medical products.\(^{100}\) Falsified facemasks, diagnostic tests and other products for the management of COVID-19 have been reported.\(^{101}\) Where a demand exists, those engaged in the manufacture and distribution of SF devices will respond, and will use online distribution channels as well as the legitimate supply chain to market their products, often accompanied by false safety and quality certification logos. Visual identification can be extremely difficult and laboratory analysis may be required to distinguish an SF product from the genuine version.

The established enforcement approach consists of prevention, detection and response. The existence of a legal framework providing for proportionate regulatory requirements and powers, including dissuasive sanctions, is essential. A regulatory system with effective oversight of importation, distribution and sale of all medical devices will help prevent SF devices reaching users and patients. Awareness-raising among consumers, health care providers and distributors can also help to minimize the threat posed by SF medical products, while retaining confidence in health technologies generally. It is important to make the general public aware of the crucial importance of buying only from reliable sources, particularly on the internet.

Effective market surveillance is important for detecting SF medical devices early. NRAs should establish mechanisms that enable and encourage the

---


reporting of suspicious medical devices. Regulator engagement with relevant stakeholders, including public and private sector organizations, law enforcement, civil society, health care providers, consumer groups and patients will lead to increased reporting and earlier detection of SF products (135, 136). In addition, new technologies (including UDI and track-and-trace systems) can provide increased assurance of the integrity of the supply chain and can also lead to the early detection of SF products.

Strengthening capacity among regulatory authorities to respond transparently, consistently and proportionately to SF products will help to maintain confidence in health systems. International collaboration and working in partnership with other stakeholders – including where necessary, law enforcement and the judiciary – will help to ensure that serious cases of falsification are dealt with in a manner commensurate with the risk to public health (25, 137–139).

8.6 **Companion diagnostics**

A “companion diagnostic” is an IVD that is essential for ensuring the safe and effective use of a corresponding medicinal product by:

- identifying, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
- identifying, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product\(^ {102}\) (44, 62).

Companion diagnostics – regulated as IVDs and abbreviated “CDx” – increase the probability of clinical success of a medicine by identifying patients carrying predictive biomarkers and disease-specific therapeutic targets and can dramatically improve the safety and/or efficacy of the treatment.

The above definition – combined with the introduction of a risk-based classification system for medical devices including IVDs based on the IMDRF system of device classification – has resulted in CDx being classified as high-risk Class C in vitro diagnostic medical devices (44). However, on an exceptional

---

\(^ {102}\) IMDRF Note 1: Companion diagnostics are essential for defining patients’ eligibility for specific treatment with a medicinal product through the quantitative or qualitative determination of specific markers identifying subjects at a higher risk of developing an adverse reaction to the medicinal product in question or identifying patients in the population for whom the therapeutic product has been adequately studied and found safe and effective. Such a biomarker or biomarkers can be present in healthy subjects and/or in patients. Note 2: Devices that are used to monitor treatment with a medicinal product in order to ensure that the concentration of relevant substances in the human body is within the therapeutic window are not considered to be companion diagnostics (http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-wng64.pdf, accessed 11 February 2023).
basis, an NRA may opt to classify individual CDx into a class other than that
determined by the IMDRF IVD classification rules.

Depending on how an NRA classifies CDx, a more complex body of
regulatory controls may apply to them.

The regulation of CDx should include clear pathways for the authorization
of clinical studies involving both products (CDx and medicine), as well as for
the coordinated review and approval of the technical documentation submitted
for market authorization. This may include the issuing of guidance regarding the
roles and responsibilities of parties bringing a CDx and medicine to market. To
ensure compliance with regulatory requirements, the following controls should
be implemented for CDx: authorization by the NRA of clinical performance
studies, market authorization, audits and post-market surveillance.

Some CDx are developed for use with specific medicines where testing
may be tied specifically to certain brand(s) of medicines. For such testing, a
combined clinical study is performed of the CDx and the medicine together.103
Regulatory requirements for the labelling of such a CDx should specify the
corresponding medicine with which it is intended to be used.

In other cases CDx are developed as standalone, where the CDx may be
used to support the use of various brands of medicine (with similar molecular
targets). Clinical studies for such CDx are performed independently. In such
cases, there is no requirement for simultaneous filing or synchronized approval
for the CDx and the medicine. The regulatory controls (pre-market authorization
and authorization of clinical performance studies) of the medicine and the device
may not necessarily be performed at the same time. However, the assessors of
the medicine and of the CDx may meet as appropriate to coordinate the two
regulatory processes.

For adverse event and incident reporting, the determination of who
should report and whether reporting to both medical device and medicine
regulators is required will be based on the apparent cause of the adverse event or
incident, and on the risk assessment performed by the respective manufacturers.
For example, any reportable event arising from the failure of the CDx (such as
inaccurate test results) should be reported to the medical device regulator. Based
on the risk assessment, if failure of the test is assessed to potentially impact the
safety and/or effectiveness of the corresponding medicine (for example, through
incorrect dosage of medicine administered to patients) then a report to the
medicine regulator by the medicine manufacturer will also be required.

Since not all countries have the capacity to perform all of the regulatory
controls discussed here – especially those in the early stages of establishing

103 For examples of CDx combined with specific medicines see: https://www.fda.gov/medical-devices/in-
vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools,
accessed 11 February 2023).
regulations for medical devices including IVDs – reliance may be used as an appropriate approach to ensure that the relevant requirements are fulfilled.

8.7 **WHO prequalification of IVDs and male circumcision devices**

Lack of access to quality health technologies, in particular IVDs, is reducing the opportunity to make progress in addressing high-burden diseases in certain countries. WHO prequalification of IVDs provides countries with appropriate technical support, tools and guidance on the provision of IVDs and laboratory services. This now includes the prequalification of male circumcision devices.\(^{104}\)

In addition to relying upon the work of reference regulatory authorities, the NRA may choose, for some medical devices, to rely upon assessments conducted for the WHO prequalification of IVDs and male circumcision devices. A focus is placed by WHO on IVDs for priority diseases (for example, HIV, malaria and hepatitis C) and their suitability for use in resource-limited settings.

WHO prequalification of IVDs and male circumcision devices is based on the use of a standardized procedure for determining whether a product meets WHO prequalification requirements. The assessment process consists of three components:

- review of the technical documentation (product dossier);
- independent performance evaluation for IVDs/evaluation of clinical studies for male circumcision devices; and
- inspection of manufacturing site(s).

Prequalification requirements are based on best regulatory practices and are designed around the essential principles of safety and performance. As such, prequalification requirements reflect recognized international standards and guidance documents – including harmonized European standards, and ISO, Clinical and Laboratory Standards Institute (CLSI) standards, and IMDRF/GHTF standards – to ensure compliance with the essential principles. As is the case for WHO-listed authorities,\(^{105}\) WHO review and prequalification assessments cover quality, safety and performance aspects.

Although prequalification requirements are thus aligned with the approach adopted by NRAs performing stringent reviews, they have also been designed in such a way as to best serve resource-limited settings. The following aspects are therefore reflected in the prequalification assessments:

- the device regulatory version marketed on the global market is assessed;

---

\(^{104}\) WHO is intending to further extend the prequalification of medical devices to other categories.

the scrutiny level reflects individual and public health risks in resource-limited settings; and

- data submitted by the manufacturer are assessed from the perspective of resource-limited settings in order to reflect the environment and users in such settings.

Countries may benefit from the programme by relying on prequalification assessment outcomes. The WHO List of Prequalified IVDs and WHO List of Male Circumcision Devices, together with reports summarizing the assessment findings, are publicly available on the WHO website.\(^{106}\)

In addition to their regulatory purposes, the findings of the WHO prequalification of IVDs and male circumcision devices, in conjunction with other procurement criteria, are typically used by United Nations agencies, WHO Member States and other interested organizations to guide procurement decisions.

8.8 **Collaborative registration procedure**

The collaborative registration procedure (CRP) was introduced to accelerate market authorization of eligible medical products in countries through information sharing between WHO and NRAs with the consent of a manufacturer of a WHO prequalified medical product. The CRP for IVDs was successfully piloted in 2019 and rolled out in May 2020 on the recommendation of the Expert Committee on Biological Standardization (140). The CRP for IVDs incorporates elements of capacity-building and regulatory harmonization. Successful application of the procedure is highly dependent on the ability and willingness of manufacturers (the applicants), NRAs and WHO to work together to meet public health goals. IVDs that are prequalified by WHO undergo a thorough evaluation (dossier assessment and laboratory performance evaluation) and a QMS audit of the manufacturing facilities according to international standards to confirm their quality, safety and performance (see section 8.7 above). Such products need to be approved by the NRAs for use in the countries for which market entry is being sought. Repeating the assessment, performance evaluation and quality audits for these products consumes scarce regulatory resources and unnecessarily prolongs the issuance of market authorization and the time needed to make them available to patients.

By leveraging assessment and inspection outputs already generated by WHO prequalification, and thereby eliminating duplicative regulatory work, the CRP speeds up the in-country market authorization of quality-assured products and contributes to their wider availability. The CRP is a typical

---

reliance mechanism based on the three key principles of voluntary regulator and manufacturer participation, confirmation of the sameness of the product of interest and ensuring confidentiality of information. NRAs are expected to issue their decision on the market authorization of a given WHO prequalified product (whether positive or negative) within 90 calendar days of regulatory review time (Fig. 8.1).

Fig. 8.1
Steps in the procedure for national registration of a WHO prequalified IVD product (140)
8.9 Emergency use listing procedure

The WHO emergency use listing (EUL) procedure\(^\text{107}\) (formerly the WHO emergency use assessment and listing (EUAL) procedure) is a risk-based procedure for assessing and listing IVDs, as well as medicines and vaccines, that have not (yet) undergone stringent regulatory assessment and that are intended for use primarily during public health emergencies of international concern (PHEICs) or other public health emergencies (see section 7.3 above). During such times, communities and public health authorities may be willing to tolerate less certainty about the safety and performance of a product given the morbidity and/or mortality associated with the disease and the urgent need for diagnostics. The EUL procedure is based on an essential set of available quality, safety and performance data, and involves the following steps:

- QMS review and plan for post-market surveillance – desktop review of the manufacturer’s QMS and its documentation, and specific manufacturing documents; and
- product dossier review – assessment of the documentary evidence of safety and performance; this evaluation is of limited scope and is intended to verify critical analytical and performance characteristics.

These reviews are conducted by one or more NRAs to which the manufacturer has made submissions, taking into account the outcomes of WHO assessments. Some submissions submitted for WHO EUL may have undergone a previous assessment through the other emergency mechanisms of a WHO-listed authority. Where this is the case, it is not the intention of WHO to undertake duplicative work if the review of the other emergency mechanism is deemed to be of a satisfactory standard.

\(^{107}\) See: [https://extranet.who.int/pqweb/vitro-diagnostics/emergency-use-listing-procedure](https://extranet.who.int/pqweb/vitro-diagnostics/emergency-use-listing-procedure), accessed 11 February 2023.)
9. Implementation

9.1 Implementation – involving stakeholders in the regulatory process

To ensure that regulatory requirements and processes meet the objectives for which they are designed, it is important to determine their effects (benefits, costs and undesirable effects) in terms of the public health, economic and social impacts that they might have.

Likewise, such regulatory processes must take into consideration the limited resources of NRAs and the importance of avoiding duplication or the creation of barriers to achieving the objectives of the regulatory system. A key element in this will be the engaging and involving of stakeholders\(^\text{108}\) in all stages of the regulatory process. Stakeholder groups are those that may be affected by the regulatory system, and include manufacturers, authorized representatives, importers, distributors, the health care sector, patients and users (4).

By working with stakeholders, policy-makers can help to determine risks and identify which regulatory controls will be the best option for addressing a public health problem. For example, the objective may best be achieved through laws (statutes and regulations), economic instruments (for example, market-based instruments such as taxes, fees, user charges, etc.), self-regulation, standards and other forms of voluntary actions, or information and education campaigns.

The introduction of medical device regulation should therefore be accompanied by the participation of stakeholders. This will facilitate, and may prevent delays in, the process of implementing regulatory controls. The NRA should establish a multidisciplinary team with experience of each stage of the life-cycle of the medical device, taking into consideration:

- who would be impacted by the regulatory controls, implementation process and policy, and in what way;
- who has or may have influence over the regulatory controls, implementation process and policy; and
- who has or may have an interest in whether regulatory control implementation is successful or unsuccessful (141).

Subsequently, a list of stakeholders should be drawn up for each of the different stages of the life-cycle – that is, pre-market, placing on the market and post-market (Fig. 9.1).

\(^{108}\) A stakeholder is any individual or group that has an interest in any decision or activity of an organization. ISO 26000 (https://iso26000.info/definitions/, accessed 7 February 2023).
The NRA multidisciplinary team should characterize each stakeholder, for example with regard to:

- **Internal/external** – internal stakeholders work within the organization promoting or implementing the policy; all other stakeholders are external.

- **Knowledge of the policy** – the exact level of knowledge that an actor has about the policy under analysis, and how each actor defines the policy in question.

- **Position** – whether the stakeholder supports, opposes or is neutral towards the policy; this will be key to establishing whether an actor will attempt to block policy implementation.

- **Vested interest** – the stakeholder’s interest in the policy, or the advantages and disadvantages that implementing the policy may bring to the stakeholder or their organization. Determining the vested interests of stakeholders will help policy-makers and managers better understand their position and address their concerns.
Alliances – organizations that collaborate to support or oppose policy. Alliances can strengthen a weak stakeholder or provide a way to influence several stakeholders by dealing with a key stakeholder.

Resources – the resources (human, financial, technological, political and others) available to the actor and its capacity to mobilize them. This is an important characteristic that is summarized in a power indicator (see next point) and will determine the degree to which the actor can support or oppose the policy.

Power – the stakeholder’s ability to affect the implementation of health reform policy.

Leadership – the willingness to initiate, convene or lead an action for or against pro-health reform policy (142).

After characterizing the stakeholders, the NRA multidisciplinary team should develop a map of stakeholders in order to evaluate their expertise, positions, importance in the process, vested interests, potential impact and alliances. This will allow the NRA to interact appropriately with stakeholders to gain their support for the implementation of the proposed regulatory controls and avoid potential misunderstandings and delays.

Public consultation may help to improve both the quality of regulation and government responsiveness to its citizens and businesses. At the technical level, the use of consultation mechanisms and the introduction of a regulatory impact analysis (4) in particular will be pivotal in collecting empirical information, measuring expectations, assessing costs and benefits, and identifying alternative policy options. At the policy level, stakeholder involvement enables a transparent policy-making process and increases social acceptance of decisions and, therefore, compliance. Stakeholder consultation is usually considered to be an integral part of ensuring regulatory quality. Stakeholders should therefore be involved when deciding, developing, reviewing, amending and soliciting feedback on:

- legislation;
- regulatory strategy, road map and policy;
- status of the NRA;
- regulations and guidelines;
- requirements for market authorization, and for post-market surveillance;
- transition period for implementing specific regulatory processes; and
- regulatory fees and timelines, and other factors as may be determined.
Involving or informing stakeholders on the above factors may lead to:

- Transparency and access to information – stakeholder consultation can increase the transparency of the rule-making process because stakeholders have access to the process itself. Additionally, consultation enables policy-makers to make use of the stakeholder's experience and knowledge. Stakeholder engagement in rule making can increase support for regulatory requirements.

- Increased familiarity and compliance – engaging stakeholders and striving for consensus can help to increase the social acceptance of regulations. It can thus contribute to greater compliance and, therefore, reduced enforcement costs. Stakeholder engagement also promotes stakeholder education on rule making, and provides stakeholders with an opportunity to increase their regulatory knowledge.

- Legitimacy and improved conflict management – stakeholder consultation provides a mechanism for managing conflicts at an early stage. Greater stakeholder engagement also has the potential to create a source of legitimacy and proof of successful governance.

- Credibility, confidence and social cohesion – stakeholder consultation can help to establish stakeholder trust and government credibility by creating new and better ways to communicate with stakeholders.

It is important to define the stages in which the different parties will be involved. Involving stakeholders in the relevant stages of implementation will allow for the development not only of policies but also of processes, avoid repetition and lead to the placing on the market and availability of compliant medical devices.

With the active and objective participation of stakeholders, the implementation process may include:

- initial creation of the NRA multidisciplinary team to evaluate which stakeholders are interested in the regulatory process to be carried out;

- generating questionnaires for stakeholders to allow the multidisciplinary team to identify those with greater or lesser impact, and greater or lesser influence;

- establishing neutral spaces that allow collaboration among stakeholders so that those involved can listen to, discuss and learn from each other;
- conducting workshops;
- sending out documents for consultation and comments; and
- holding specific technical roundtables for each stage of the product life-cycle, allowing the appropriate stakeholders to be involved for each topic (143).

As part of GRP it is important to control the influence of stakeholders so that the development and implementation of regulatory controls is not prejudiced or biased by one or more of the stakeholders.

9.2 Implementation – developing a road map

The establishment of a new national medical device regulatory system, or significant changes to an existing system, requires thorough and careful planning. A comprehensive outline or “road map” is a visual way to quickly communicate a plan or strategy and will be helpful in its planning and implementation.

In preparing a road map, the first step will be to carry out a gap analysis (see section 5.2 above) in which the current local situation is compared with established medical device regulatory systems (benchmarks) based on WHO recommendations (3, 4, 5, 55, 144) and on international harmonization consensus guidance documents (64). It is important to consider the views of local stakeholders, including patient representatives. In addition, consideration should be given to public health priority needs, characteristics of the national medical devices market, national burden of disease, demographic trends, level and characteristics of economic development, size of the country, supply chain and the nature of the medical devices in the market.

Based on the findings of the gap analysis, the NRA can then identify priorities and the regulatory functions to be implemented in the pre-market, placing on the market and post-market stages.

It is generally not feasible to make the transition from an unregulated market to a highly regulated market in one step or in a very short time. This process requires a significant increase in the size and knowledge of the NRA, education of the regulated industry and health product purchasers and users, as well as high-level political commitment and long-term financial support. To achieve the above, WHO recommends that the implementation of such regulation be carried out in stages. At each stage, the principles of GRP for medical products should be applied (4). This GMRF outlines the basic-level regulatory controls that should be effectively implemented first. As resources permit, and according to national policy priorities, expanded-level regulatory controls may be implemented on the foundation of the basic-level regulatory controls.
The general and specific objectives that the NRA must meet in the implementation of a new or changed regulatory system should be outlined in an implementation plan. It should identify possible regulatory, institutional and/or technical changes in the processes of the NRA.

The development of a prioritization matrix (see Table 9.1) in which the consequences of individual risks are mapped to their probability of occurrence will make it possible to prioritize the identified objectives and actions (145).

Table 9.1
An example of a “probability–impact” matrix for risk ranking (145)

<table>
<thead>
<tr>
<th></th>
<th>very low consequences</th>
<th>low consequences</th>
<th>medium consequences</th>
<th>high consequences</th>
<th>very high consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>very low probability</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>medium risk</td>
</tr>
<tr>
<td>low probability</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>medium risk</td>
<td>medium risk</td>
</tr>
<tr>
<td>medium probability</td>
<td>low risk</td>
<td>low risk</td>
<td>medium risk</td>
<td>medium risk</td>
<td>critical risk</td>
</tr>
<tr>
<td>high probability</td>
<td>low risk</td>
<td>medium risk</td>
<td>medium risk</td>
<td>critical risk</td>
<td>critical risk</td>
</tr>
<tr>
<td>very high probability</td>
<td>low risk</td>
<td>medium risk</td>
<td>critical risk</td>
<td>critical risk</td>
<td>critical risk</td>
</tr>
</tbody>
</table>

Such a matrix may be used by policy-makers and the NRA in several ways when setting national priorities for the implementation of regulatory controls:

- The likelihood and severity of the national burden of disease may dictate regulatory priorities. For example, a high prevalence of a particularly severe disease or condition may justify a higher priority for access to certain medical devices, and development of the requisite regulatory and scientific expertise. If SF higher risk medical devices are known to be widespread, then a higher priority could be given to listing, registration, import controls and market surveillance.

The stringency of regulatory controls should be proportionate to the consequence of the potential harm to be prevented. For harms of low consequence, even if relatively common, voluntary compliance by regulated medical device suppliers may be adequate. However, more stringent mandatory controls will be justified by potential harms with very severe consequences, even if infrequent. If resources prevent full implementation of a regulatory system for all devices at one time, a risk assessment may support the phased introduction of controls on higher risk-class devices before those for lower risk-class devices.

Organizational risks include lack of consistent high-level political support, insufficient funding, misallocation of resources, inability to recruit and retain appropriately qualified staff, inadequate information systems or facilities, and loss of credibility and reputation as an effective enforcement body. The failure of an NRA to implement effective market surveillance mechanisms and/or of device manufacturers to properly report adverse events and incidents will impair the ability of the NRA to properly monitor and evaluate emerging device-related risks.

At this point, the necessary resources – human, technical, facilities, information technologies and economic – must be estimated. A realistic timeline must be established for the stepwise implementation of the plan in the short, medium and long term. Based on the proposed prioritization, detailed work plans must be prepared, along with the high-level road map laying out outcomes, responsibilities and timelines (Table 9.2).

The implementation plan will require continuous monitoring and evaluation of compliance with its objectives. To enable this, it is recommended that technical and other guidance documents are developed to make the established guidelines known to the stakeholders involved. It is recommended that these documents are based on international regulatory guidance adapted to the local context. The road map must also be updated on a regular basis.
### Table 9.2
Example of a high-level road map

<table>
<thead>
<tr>
<th>Objective</th>
<th>Responsible entity</th>
<th>Outcome/indicator</th>
<th>Information source</th>
<th>Interested stakeholder</th>
<th>Communication</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adopt law and regulations</td>
<td>MoH</td>
<td>Adopted legislation</td>
<td>Parliament</td>
<td>Manufacturers Importers Patients Health care sector</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pre-market</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Define pre-market conformity</td>
<td>NRA</td>
<td>Regulations and guidance for stakeholders</td>
<td>NRA</td>
<td>Manufacturers Importers Authorized representatives</td>
<td>Meetings Workshops Internet</td>
<td></td>
</tr>
<tr>
<td>System and resources for pre-market assessment</td>
<td>NRA</td>
<td>Number of market authorizations</td>
<td>NRA</td>
<td>Manufacturers Importers Authorized representatives</td>
<td>Meetings Workshops Internet</td>
<td></td>
</tr>
<tr>
<td><strong>Placing on the market</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oversight: registration of establishments</td>
<td>NRA</td>
<td>Number of establishment registrations</td>
<td>NRA</td>
<td>Manufacturers Importers Distributors</td>
<td>Meetings Mailings Internet</td>
<td></td>
</tr>
<tr>
<td>Oversight: listing of medical devices</td>
<td>NRA</td>
<td>Number of medical devices listed</td>
<td>NRA</td>
<td>Manufacturers Importers Distributors Authorized representatives</td>
<td>Meetings Mailings Internet</td>
<td></td>
</tr>
<tr>
<td>Objective</td>
<td>Responsible entity</td>
<td>Outcome/indicator</td>
<td>Information source</td>
<td>Interested stakeholder</td>
<td>Communication</td>
<td>Timeline</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>------------------------</td>
<td>---------------</td>
<td>----------</td>
</tr>
<tr>
<td>Post-market</td>
<td>NRA</td>
<td>Number of reports of incidents reviewed compared to neighbouring countries</td>
<td>NRA</td>
<td>Manufacturers</td>
<td>Meetings</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Distributors</td>
<td>Mailings</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Authorized representatives</td>
<td>Internet</td>
<td></td>
</tr>
<tr>
<td>Establish system for review of adverse events and incidents reported by manufacturers</td>
<td>NRA</td>
<td>Number of notices issued compared to neighbouring countries</td>
<td>NRA</td>
<td>Manufacturers</td>
<td>Internet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Authorized representatives</td>
<td>Mailings</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Health care sector</td>
<td>Media</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
9.3 Implementation – regulatory capacity-building

The NRA should ensure the quality and integrity of the regulatory processes through the recruitment and retention of people with the necessary, skills, knowledge and experience. Capacity-building generally includes increasing organizational capacity, physical and communications infrastructure, and individual knowledge and skills. Regulatory capacities are related to the technical and scientific competence necessary to adapt to developments in national and international regulatory practices and standards. Regulatory capacities should also sufficiently support NRAs in implementing the legal framework, guidelines and procedures. Policies and measures for personal and career development (for example, training programmes or competitive remuneration schemes) are critical in attracting and retaining competent staff (4).

Due to the nature of their technologies, complex classification, and the wide and diverse range of product categories, medical devices including IVDs require knowledge and skills different to those needed for medicines. The NRA should be able to assess the quality, safety and performance of all product categories of medical devices including IVDs, calling upon outside experts and/or reliance on the work of other regulatory authorities as necessary.

Staff teams working in this area must be multidisciplinary to allow the NRA to assess medical devices for compliance with the national regulatory requirements during non-emergency situations, emergency situations, and when using reliance or recognition.

The development of regulatory capacities should begin by establishing regulatory processes for medical devices and identifying the associated competencies and skills required by the personnel involved. Regulatory capacities should be strengthened through institutional training programmes for developing and monitoring these competencies and skills.

The WHO global competency framework for regulators of medical products describes the competencies and underlying knowledge and skills needed (60, 146). Each NRA should specify the skills required in each position in the institutional organizational chart as mapped to these framework competencies.

9.3.1 Training plan for NRA staff

The training of NRA staff in regulatory functions must be aligned and maintained according to the competencies to be developed and implemented by the NRA. The NRA can then generate annual programmes based on the mapping of training needs, including training on specific topics. Based on this mapping, it is recommended that annual training plans are established for each staff member to address the specific topics to be covered. The annual training plans should be reviewed at least once every year (2).
The NRA should establish procedures for the formal selection, training, approval and assigning of personnel involved in regulatory reviews, QMS audits, market surveillance and enforcement functions (57, 59). The NRA should maintain evidence that the personnel have the required skills and competencies. Formal and informal exchanges of knowledge and experience with regulatory experts from other NRAs will promote collaboration and harmonization that may facilitate the use of reliance.

9.3.3.1 Competencies, skills and expertise
The eight general core competencies described in Table 9.3 should be evaluated depending on the objectives of the established programmes. The NRA should undertake continuous evaluation and monitoring programmes for the competencies, skills and expertise that will underpin the technical skills required of its staff.

Table 9.3
Core competencies for regulators (57)

<table>
<thead>
<tr>
<th>Competency</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Context analysis</td>
<td>• understanding of the role of regulation as a tool of government</td>
</tr>
<tr>
<td></td>
<td>• ability to work within the wider regulatory framework</td>
</tr>
<tr>
<td></td>
<td>• ability to work towards your organization’s regulatory objectives</td>
</tr>
<tr>
<td></td>
<td>• ability to work with the legislation relevant to your regulatory function(s)</td>
</tr>
<tr>
<td></td>
<td>• ability to work within your organization’s regulatory policies and procedures</td>
</tr>
<tr>
<td></td>
<td>• understanding of the role and responsibilities of partner organizations</td>
</tr>
<tr>
<td>Risk assessment</td>
<td>• ability to assess regulatory risks</td>
</tr>
<tr>
<td></td>
<td>• ability to gather, analyze, use and share data to inform risk assessment</td>
</tr>
<tr>
<td></td>
<td>• ability to use risk assessment to guide your activities</td>
</tr>
<tr>
<td></td>
<td>• understanding of risk management in a business context</td>
</tr>
<tr>
<td>Understanding those you regulate</td>
<td>• understanding of the current business environment and the business sector(s) regulated</td>
</tr>
<tr>
<td></td>
<td>• understanding of how regulation and the way it is enforced can impact on the business communities and individual businesses regulated</td>
</tr>
<tr>
<td></td>
<td>• understanding of the factors that affect business approaches to compliance</td>
</tr>
<tr>
<td></td>
<td>• ability to engage constructively with business</td>
</tr>
<tr>
<td></td>
<td>• ability to tailor your approach to the businesses and individuals that you interact with</td>
</tr>
</tbody>
</table>
Table 9.3 continued  

<table>
<thead>
<tr>
<th>Competency</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning of activities</td>
<td>• ability to act within your role and area(s) of responsibility</td>
</tr>
<tr>
<td></td>
<td>• ability to make appropriate intervention choices, drawing on your understanding of the context in which you operate, of those that you regulate, and of the use of risk-based approaches so as to have the greatest impact</td>
</tr>
<tr>
<td></td>
<td>• ability to work effectively with other organizations</td>
</tr>
<tr>
<td></td>
<td>• ability to plan your work, and that of your team, so as to meet your responsibilities efficiently</td>
</tr>
<tr>
<td>Compliance</td>
<td>• ability to prepare appropriately for checks on compliance</td>
</tr>
<tr>
<td></td>
<td>• ability to conduct checks in a proportionate manner</td>
</tr>
<tr>
<td></td>
<td>• ability to be responsive to the circumstances encountered</td>
</tr>
<tr>
<td></td>
<td>• ability to make informed assessments of compliance and risk</td>
</tr>
<tr>
<td></td>
<td>• ability to follow-up on checks of compliance in an appropriate manner</td>
</tr>
<tr>
<td>Support for compliance</td>
<td>• understanding of the need for compliance support among those you regulate</td>
</tr>
<tr>
<td></td>
<td>• ability to promote the importance of compliance, and your organization’s role in supporting compliance</td>
</tr>
<tr>
<td></td>
<td>• ability to communicate in appropriate ways to suit the circumstances</td>
</tr>
<tr>
<td></td>
<td>• ability to provide the information and guidance that is needed by those you regulate</td>
</tr>
<tr>
<td></td>
<td>• ability to provide the tailored advice that is needed by those you regulate, where appropriate</td>
</tr>
<tr>
<td>Management of non-compliance</td>
<td>• ability to select proportionate responses to non-compliance and potential non-compliance</td>
</tr>
<tr>
<td></td>
<td>• ability to communicate effectively with businesses that have failed to comply</td>
</tr>
<tr>
<td></td>
<td>• ability to conduct thorough investigations of non-compliance and allegations of non-compliance</td>
</tr>
<tr>
<td></td>
<td>• ability to prepare and implement effective responses to non-compliance</td>
</tr>
<tr>
<td></td>
<td>• ability to provide appropriate support for those adversely affected by non-compliance</td>
</tr>
<tr>
<td>Evaluation</td>
<td>• ability to monitor and report on your activities and performance</td>
</tr>
<tr>
<td></td>
<td>• ability to evaluate your activities in relation to your regulatory objectives and your organization’s strategic priorities</td>
</tr>
<tr>
<td></td>
<td>• understanding of the value of feedback from those you regulate, and the beneficiaries of regulation in informing future activities</td>
</tr>
</tbody>
</table>
9.3.3.2 Exploring training opportunities

Sources of training include workshops, courses, webinars, worktables and discussion, as well as evaluations of regulatory processes that indicate the improvements to be made in specific areas. E-learning and digital information resources will facilitate access to updated training options (Fig. 9.2).

The NRA may choose to create alliances for capacity development with institutions that can support the strengthening and development of regulatory capacities, both at national and international level. Through regional harmonization initiatives or regional collaboration, regulators may opt to create regional Centres of Excellence (CoEs) to facilitate the training of regulators.

Several institutions and NRAs have generated programmes that focus not only on the NRA but are also applicable to the regulated industry – through innovation centres for educational purposes, organizing of virtual courses, cooperation agreements and inter-institutional training on building capacities.

To access expert input the following options may be considered:

- external expert policy;
- CABs;
- international organizations such as WHO;
- regional harmonization initiatives such as IMDRF,\textsuperscript{110} GHWP,\textsuperscript{111} AMDF,\textsuperscript{112} APEC RHSC;\textsuperscript{113}
- internal portfolio of national and international experts; and
- academic institutions.

Such sources may provide expertise that can guide the actions of regulators within the NRA, and help to achieve a greater understanding of medical devices including IVDs and their regulation, especially in relation to new technologies.

Once implementation of the planning steps outlined above has begun, the NRA, under the oversight of the legislature or parliament, should periodically publish reports on the progress made towards policy goals and on the effectiveness of the measures taken. Such progress and effectiveness should be measured against national priorities and performance measurements, not only with regard to plan milestones, but also to indicate the compliance of regulated industry and the development of regulatory capacity.

The WHO GBT and GBT + medical devices (2, 3) were developed to enable WHO and NRAs to identify areas of strength as well as areas for improvement, facilitate the formulation of an institutional development plan (IDP) to build upon strengths and address the identified gaps, aid in the prioritization of investments in IDP implementation and to help monitor progress. The GBT also incorporates the concept of “maturity level” (adapted from ISO 9004), allowing WHO and NRAs to assess the overall maturity of the regulatory system on a scale of 1 (existence of some elements of a regulatory system) to 4 (operating at an advanced level of performance and continuous improvement).

Although it is acknowledged that not all countries will be able to move at the same speed or devote the same levels of resources, systematic assessment and continued progress in this area will lead to greater public confidence in the regulation – and safety, performance and quality – of medical devices including IVDs used in health systems.

\textsuperscript{111} GHWP – \url{http://www.ahwp.info}, accessed 12 February 2023.
\textsuperscript{112} AMDF – \url{http://www.amdfnra.org}, accessed 12 February 2023.
Authors and acknowledgments

This revision of the GMRF was undertaken by the WHO Department of Regulation and Prequalification, Regulation and Safety Unit, under the direction of A. Sitta Kiio, World Health Organization, Switzerland, supported by: J. Hansen, consultant, the Netherlands; and W. Urassa, consultant, United Republic of Tanzania. Support for the revision process was also provided by: A. Bach, H. Sillo, J. Dong, M. Valentin, S. Azatyan and Y. Maryuningsih, World Health Organization, Switzerland; A. Lemgruber, A. Porras and N. Enriquez Rodriguez, WHO Regional Office for the Americas, the USA; D. Pirgari, WHO Regional Office for Europe, Denmark; M. Ameel, WHO Regional Office for South-East Asia, India; D. Rodrigues, consultant, Switzerland; and O. Pineda, consultant, El Salvador. Guidance and technical support were provided by the following members of the WHO Steering Group: A. Velazquez, A. Keyter, A. Sands, M. Santos, M. Refaat and R. Ostad Ali Dehaghi, World Health Organization, Switzerland.

K. Benti, Ethiopian Food and Drug Administration, Ethiopia; M. Atem, Drug and Food Control Authority, South Sudan; N. Condé, Direction Nationale de la Pharmacie et du Médicament, Guinea; O. Adekunle-SEGUN, National Agency for Food and Drug Administration and Control, Nigeria; P. Shah and V. Ferguson, Medicines and Healthcare products Regulatory Agency, the United Kingdom; P. Wairimu, Pharmacy and Poisons Board, Kenya; R. Geertsma, National Institute for Public Health and the Environment, the Netherlands; R. Audu, Nigerian Institute of Medical Research, Nigeria; S. Rashid, Zanzibar Food and Drug Agency, United Republic of Tanzania; S. Kanako and T. Atsushi, Ministry of Health, Labour and Welfare, Japan; S.D. Thangavelu, consultant, Malaysia; S. Kisoma, Tanzania Medicines and Medical Devices Authority, United Republic of Tanzania; S.O. Yeboah, West African Health Organization, Burkina Faso; T. Reed, consultant, the USA; T. Quan, Global Harmonization Working Party; and W. Samukange, Paul-Ehrlich-Institut, Germany.

We also gratefully acknowledge the contributions of members of the African Medical Devices Forum (AMDF), Global Harmonization Working Party (GHWP) and the International Medical Device Regulators Forum (IMDRF) who developed the documents that formed the basis of the proposed GMRF document (WHO/BS/2022.2425). Acknowledgement is also given to B. Streef, the Netherlands; M. Gropp, the USA; and all respondents from industry, professional organizations and nongovernmental organizations during public consultations held during the development of document WHO/BS/2022.2425.

Further changes were made to document WHO/BS/2022.2425 by the Expert Committee on Biological Standardization.

References


Annex 3

contains%20elements%20of%20the%20medical%20device%20regulatory%20authorities%20of%20ASEAN%20member%20c, accessed 28 February 2023).


143. Guía metodológica para la implementación de la evaluación. Ex Post de la regulación. Tomar decisiones de manera eficiente, a partir de la evidencia (https://colaboracion.dnp.gov.co/CDT/ModernizacionEstado/ERel/Guia_Metodol%C3%B3gica_Evaluaci%C3%B3n_ExPost.pdf, accessed 28 February 2023).


# Appendix 1

## Hierarchy of regulation

<table>
<thead>
<tr>
<th>Level</th>
<th>Brief description</th>
<th>Examples</th>
<th>Examples of subject matter regulated in the field of medical devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary legislation</td>
<td>Law, or executive law – as used in this GMRF refers to binding and enforceable legislation, usually adopted at the level of individual countries by their respective legislatures and/or executives.</td>
<td>Act of parliament, bill, statutory law, EU Regulation, ordinance, decree, executive order.</td>
<td>Establishment of the NRA including enforcement power; reliance and recognition; definition of a medical device; placing on the market; market withdrawal; classification of medical devices; essential principles of safety and performance; requirement for a quality management system (QMS); adverse event and incident reporting; clinical investigations; listing of medical devices; registration of establishments; process to recognize standards.</td>
</tr>
<tr>
<td>Secondary legislation</td>
<td>A form of law – as used in this GMRF refers to written instruments that are binding and enforceable and are issued by the regulatory (executive) authority.</td>
<td>Regulations, schedule</td>
<td>Requirements for reliance; conduct of QMS audits; adverse event and incident reporting; criteria for recalls and field safety corrective actions (FSCAs); classification rules; responsibilities of an authorized representative.</td>
</tr>
</tbody>
</table>
### Table continued

<table>
<thead>
<tr>
<th>Level</th>
<th>Brief description</th>
<th>Examples</th>
<th>Examples of subject matter regulated in the field of medical devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidelines(^a)</td>
<td>Guidance documents that refer generally to non-binding normative documents issued by the NRA, which offer guidance on recommended practices. They allow for scientifically justified, alternative approaches and translation of a regulatory generally acceptable approach. Guidelines set out the current thinking, practices, explanations and expectations of the NRA, but compliance with such documents is not mandatory. The manufacturer (or other party) may choose not to apply or comply with such guidance, but must provide a rationale for, and justify, deviation from that guidance.</td>
<td>Technical standards, recommendations.</td>
<td>Guidance on interpretation and application of the classification rules; interpretation of the meaning of “primary intended mode of action” (related to the definition of “medical device”); specific labelling requirements; good laboratory practice; good clinical practice.</td>
</tr>
</tbody>
</table>

\(^a\) Note that the term “Guidelines” as used above does not refer to guidelines in the sense of the WHO handbook for guideline development. Geneva: World Health Organization; 2014.
Appendix 2

Further reading


Annex 4

New and replacement WHO international reference standards for biological products

The provision of global measurement standards is a core normative WHO activity. WHO international reference standards are widely used by manufacturers, regulatory authorities and academic researchers in the development and evaluation of biological products. The timely development of new reference standards is crucial in harnessing the benefits of scientific advances in new biologicals and in vitro diagnosis. At the same time, management of the existing inventory of WHO international reference standards requires an active and carefully planned programme of work to replace established materials before existing stocks are exhausted.

The considerations and guiding principles used to assign priorities and develop the programme of work in this area have previously been set out as WHO Recommendations. In order to facilitate and improve transparency in the priority-setting process, a simple tool was developed as Appendix 1 of these WHO Recommendations. This tool describes the key considerations taken into account when assigning priorities, and allows stakeholders to review and comment on any new proposals being considered for endorsement by the WHO Expert Committee on Biological Standardization.

A list of current WHO international reference standards for biological products is available at: https://www.who.int/health-topics/Biologicals#tab=tab_1.

At its meetings held via video conference on 24–28 October 2022, the WHO Expert Committee on Biological Standardization made the changes shown below to the previous list. Each of the WHO international reference standards shown in this table should be used in accordance with their instructions for use (IFU).

Additions

<table>
<thead>
<tr>
<th>Material</th>
<th>Unitage</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biotherapeutics other than blood products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 IU/ampoule for IOP activity</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td></td>
<td>1000 IU/ampoule for ADCC activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 IU/ampoule for EGFR binding activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 IU/ampoule for FcγRIIa(V158) binding activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 IU/ampoule for FcγRI binding activity</td>
<td></td>
</tr>
<tr>
<td>Infliximab antibodies</td>
<td>Material A (NIBSC code 19/234)</td>
<td>First WHO International Reference Panel</td>
</tr>
<tr>
<td></td>
<td>50 000 IU/ampoule for binding antibody activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 000 IU/ampoule for neutralizing antibody activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Material B (NIBSC code 19/232)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No unitage assigned</td>
<td></td>
</tr>
<tr>
<td>Interleukin-6 (human, recombinant)</td>
<td>143 000 IU/ampoule</td>
<td>Second WHO International Standard</td>
</tr>
<tr>
<td><strong>Blood products and related substances</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood coagulation factor XIII (plasma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.04 IU/ampoule for overall potency</td>
<td>Second WHO International Standard</td>
</tr>
<tr>
<td></td>
<td>0.98 IU/ampoule for A2B2 antigen content</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.92 IU/ampoule for total FXIII-B subunit content</td>
<td></td>
</tr>
<tr>
<td><strong>Cell, tissue and gene therapy products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lentiviral vector copy number for quantitative PCR</td>
<td>6.89 log_{10} copies/ampoule</td>
<td>WHO International Reference Reagent</td>
</tr>
<tr>
<td></td>
<td>(95% CI = 6.81–6.98 log_{10})</td>
<td></td>
</tr>
</tbody>
</table>

115 Unless otherwise indicated, all materials are held and distributed by the Medicines and Healthcare products Regulatory Agency, Potters Bar, Herts, EN6 3QG, the United Kingdom.
<table>
<thead>
<tr>
<th>Material</th>
<th>Unitage</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lentiviral vector copy number for digital PCR</td>
<td>$6.75 \log_{10} \text{copies/ampoule}$ (95% CI = 6.71–6.79 $\log_{10}$)</td>
<td>WHO International Reference Reagent</td>
</tr>
<tr>
<td><strong>In vitro diagnostics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibodies to chikungunya virus</td>
<td>500 IU/vial</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td><strong>Standards for use in public health emergencies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARS-CoV-2 antigen</td>
<td>5000 IU/ampoule</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td>Anti-SARS-CoV-2 immunoglobulin</td>
<td>356 IU/ampoule</td>
<td>Second WHO International Standard</td>
</tr>
<tr>
<td>Antibodies to SARS-CoV-2 variants of concern</td>
<td>4250 IU/ampoule</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td>Antibodies to SARS-CoV-2 variants of concern</td>
<td>No unitage assigned</td>
<td>First WHO International Reference Panel</td>
</tr>
<tr>
<td><strong>Vaccines and related substances</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-human papillomavirus type 6 serum</td>
<td>7 IU/ampoule</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td>Anti-human papillomavirus type 11 serum</td>
<td>6 IU/ampoule</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td>Anti-human papillomavirus type 31 serum</td>
<td>3 IU/ampoule</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td>Anti-human papillomavirus type 33 serum</td>
<td>8 IU/ampoule</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td>Anti-human papillomavirus type 45 serum</td>
<td>2 IU/ampoule</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td>Anti-human papillomavirus type 52 serum</td>
<td>14 IU/ampoule</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td>Anti-human papillomavirus type 58 serum</td>
<td>20 IU/ampoule</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td>Tetanus antitoxin for use in flocculation test (equine)</td>
<td>No unitage assigned</td>
<td>WHO International Reference Reagent</td>
</tr>
<tr>
<td>Material</td>
<td>Unitage</td>
<td>Status</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Antibodies to rabies virus</td>
<td>164 IU/ampoule for RFFIT and FAVN</td>
<td>Third WHO International Standard</td>
</tr>
<tr>
<td></td>
<td>128 IU/ampoule for antibody binding methods</td>
<td></td>
</tr>
<tr>
<td>D-antigen content of type 1 poliovirus</td>
<td>No unitage assigned</td>
<td>WHO International Reference Reagent</td>
</tr>
<tr>
<td>D-antigen content of type 2 poliovirus</td>
<td>No unitage assigned</td>
<td>WHO International Reference Reagent</td>
</tr>
<tr>
<td>D-antigen content of type 3 poliovirus</td>
<td>No unitage assigned</td>
<td>WHO International Reference Reagent</td>
</tr>
<tr>
<td>D-antigen content of types 1, 2 and 3 polioviruses</td>
<td>No unitage assigned</td>
<td>WHO International Reference Reagent</td>
</tr>
</tbody>
</table>
The World Health Organization was established in 1948 as a specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective and reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications.

The Organization seeks through its publications to support national health strategies and address the most pressing public health concerns of populations around the world. To respond to the needs of Member States at all levels of development, WHO publishes practical manuals, handbooks and training material for specific categories of health workers; internationally applicable guidelines and standards; reviews and analyses of health policies, programmes and research; and state-of-the-art consensus reports that offer technical advice and recommendations for decision-makers. These books are closely tied to the Organization's priority activities, encompassing disease prevention and control, the development of equitable health systems based on primary health care, and health promotion for individuals and communities. Progress towards better health for all also demands the global dissemination and exchange of information that draws on the knowledge and experience of all WHO's Member countries and the collaboration of world leaders in public health and the biomedical sciences.

To ensure the widest possible availability of authoritative information and guidance on health matters, WHO secures the broad international distribution of its publications and encourages their translation and adaptation. By helping to promote and protect health and prevent and control disease throughout the world, WHO's books contribute to achieving the Organization's principal objective – the attainment by all people of the highest possible level of health.

The WHO Technical Report Series makes available the findings of various international groups of experts that provide WHO with the latest scientific and technical advice on a broad range of medical and public health subjects. Members of such expert groups serve without remuneration in their personal capacities rather than as representatives of governments or other bodies; their views do not necessarily reflect the decisions or the stated policy of WHO.

To purchase WHO publications, please contact: WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; email: bookorders@who.int; order online: www.who.int/bookorders.

Website: https://www.who.int/health-topics/Biologicals#tab=tab_1

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

WHO Expert Committee on Biological Standardization
Seventy-fifth report.
WHO Technical Report Series, 1043, 2022 (xii + 252 pages)

WHO Expert Committee on Biological Standardization
Seventy-fourth report.

WHO Expert Committee on Biological Standardization
WHO Technical Report Series, No. 1030, 2021 (xvii + 269 pages)

WHO Expert Committee on Biological Standardization
Seventy-first report.
WHO Technical Report Series, 1028, 2021 (xii + 102 pages)

WHO Expert Committee on Biological Standardization
Sixtieth report.
WHO Technical Report Series, No. 1024, 2020 (xvi + 380 pages)

WHO Expert Committee on Biological Standardization
Sixty-ninth report.
WHO Technical Report Series, No. 1016, 2019 (xviii + 591 pages)

WHO Expert Committee on Biological Standardization
Sixty-eighth report.
WHO Technical Report Series, No. 1011, 2018 (xvi + 380 pages)

WHO Expert Committee on Biological Standardization
Sixty-seventh report.

WHO Expert Committee on Biological Standardization
Sixty-sixth report.
WHO Technical Report Series, No. 999, 2016 (xix + 267 pages)
This report presents the recommendations of a WHO Expert Committee commissioned to coordinate activities leading to the adoption of international recommendations for the production and control of vaccines and other biological products used in medicine, and the establishment of international biological reference materials.

Following a brief introduction, the report summarizes a number of issues brought to the attention of the Committee at its meeting held virtually in October 2022. Of particular relevance to manufacturers and national regulatory authorities are the discussions held on the development and adoption of new and revised WHO Recommendations, Guidelines and guidance documents. Following these discussions, the following two documents were adopted on the recommendation of the Committee: (a) Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated); and (b) WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices.

Subsequent sections of the report provide information on the current status, proposed development and establishment of international reference materials in the areas of: biotherapeutics other than blood products; blood products and related substances; cell, tissue and gene therapy products; in vitro diagnostics; standards for use in public health emergencies; and vaccines and related substances.

A series of annexes is then presented which includes an updated list of all WHO Recommendations, Guidelines and other documents related to the manufacture, quality control and evaluation of biological products (Annex 1). The above two WHO documents adopted on the advice of the Committee are then presented as part of this report (Annexes 2 and 3). Finally, all new and replacement WHO international reference standards for biological products established during the October 2022 meeting are summarized in Annex 4. The updated full online catalogue of WHO international reference standards is available at: https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/catalogue.